THE SIGNIFICANCE AND CLASSIFICATION OF FAT-EMBOLISM

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ALTHOUGH pulmonary fat-embolism is very common after injury, its clinical significance has been greatly overestimated. On the other hand systemic embolism is less frequent but more likely to be significant, mainly because of cerebral involvement. Nevertheless, fat-embolism continues to be classified clinically into pulmonary and cerebral forms, suggesting that pulmonary emboli produce symptoms; and often a cardiac form is added. This confusion has arisen (1) because cardiovascular effects of hæmorrhage and oligæmia have often been attributed to fat-embolism; (2) because non-embolic pulmonary complications have been considered to be of embolic origin; and (3) because the respiratory symptoms and tachycardia, which are often part of unequivocal clinical embolism, have little to do with emboli in the lungs. Myocardial embolism is being studied, but provisional results show that it, and its possible effects, are overestimated.

The present analysis is based on data of three kinds—a clinicopathological study of 100 injured cases reaching necropsy, a later group of special cases which also died, and a study of 20 patients with clinically diagnosed systemic embolism. The picture and severity of systemic embolism varies widely from rapidly fatal fulminating forms, diagnosed only at necropsy, to mild, almost subclinical, effects. Failure to appreciate this is partly responsible for difficulties in diagnosis, and for the widely divergent views as to prognosis.

Pulmonary Fat-embolism

Heavy pulmonary embolism is closely related to the severity of injury, and in particular to the multiplicity of fractures and the speed of dying (Sevitt 1957, Emson 1958); but pathological, clinical, and experimental evidence now indicates that even histologically gross embolism (naturally occurring) is unlikely to be important.

The pulmonary congestion, œdema, small hæmorrhages, and foci of collapse, which are said to result from capillary blockage and endothelial anoxia, are mainly due to non-embolic causes; thoracic, abdominal, and cerebral trauma all tend to produce pulmonary congestion and œdema, whilst terminal and agonal effects are often difficult to eliminate. The weight of the lungs and the histological degree of embolism do not correlate (Scully 1956), whilst the fluid nature of the embolic fat at body temperature raises doubts as to whether the alveolar capillaries are completely blocked (Wilson 1946).

In previously healthy patients dying during the first few days after injury respiratory distress is not common, even though pulmonary embolism may be considerable—provided that cerebral and thoracic injuries are absent, that blood-loss has been corrected by transfusion, and that cerebral fat-embolism is not present. Further, many cases of clinical systemic embolism do not have respiratory symptoms, and yet systemic embolism is nearly always associated with a heavy degree of pulmonary fat-embolism at necropsy (Sevitt 1957, Emson 1958).

Experimentally the intravenous injection of fat can produce acute respiratory distress, venous congestion, and even death; but, as Scriba (1880) and Cohnheim (1889) first pointed out, the lungs then show a very heavy degree of embolism which is never seen in man. The dose needed to produce these effects is high (Lehman and Moore 1927, Harris et al. 1939, Scuderi 1941), and Armin and Grant (1951) showed that the fat extractable from the lungs of patients dying with gross embolism is only a fraction of what would be required.

Serious effects were produced if shock or blood-loss was also present (Gold and Loeffler 1923, Green and Stoner 1950, Harman and Ragaz 1950, Whiteley 1954); but again the amount of fat injected was much greater than that necessary to produce embolism comparable to gross embolism in man. Armin and Grant (1951) showed that, when this dose was given to rabbits which were also subjected to considerable hæmorrhage, it did not add to the illness or the mortality; nor did the injection of fat into bled animals hinder the beneficial response to blood-transfusion.

It seems reasonable to conclude that pulmonary fat-embolism does not cause significant symptoms or produce serious lung changes in previously healthy subjects, and that it is not responsible for death even in patients with shock or hæmorrhage. The lack of effect is presumably related to the large functional reserves and enormous capillary bed within the lungs, and to the fluid nature of the emboli.

Systemic Fat-embolism

A full analysis of systemic embolism must include cases which were found at necropsy but unsuspected during life, and those which were diagnosed clinically, some of whom die and reach necropsy (see Sevitt 1959).

At necropsy, systemic embolism (based on fat-emboli in vessels of the brain or in glomeruli, or both) is less common than the pulmonary form with which it is always associated.

In a series of 100 necropsies at the Birmingham Accident Hospital, none of whom were suspected of having clinical embolism, 24% had systemic embolism and 89% had pulmonary embolism, and all those with systemic emboli had pulmonary emboli (Sevitt 1957, 1959, Emson 1958). Systemic embolism was found in 59% of the 32 patients with numerous pulmonary emboli, but in only 9% of the 57 patients with few or moderate numbers of emboli in the lungs. Systemic embolism had occurred in 45% of those with severe bony injuries, but in only 7% of those with mild or moderate bony injuries. In a third of the cases systemic embolism was relatively heavy, and all those patients had gross pulmonary embolism and multiple fractures.

Analysis of the case-records showed that cases with systemic embolism at necropsy could be divided into those which had had unexplained cerebral and other symptoms consistent with fat embolism (7 cases), and those without significant symptoms (17 cases). In 4 cases cerebral embolism was considered to be the main cause of death; symptoms regarded as significant were unexplained drowsiness, coma or failure to recover consciousness after anæsthesia, and unexplained cerebral irritation such as convulsions, athetoid movements, and epilepsy when there was no evidence of cerebral injury. The number of such cases was probably underestimated because cerebral embolism was possibly significant in some of those with traumatic cerebral

contusion. Other workers have made similar correlations: Grant and Reeve (1951) found histological systemic embolism in 13 cases dying after limb injury, 5 of which had relevant cerebral effects, whilst Scully (1956) concluded that in only 1 of his 19 cases was systemic embolism the cause of death.

I have kept in mind the clinical difficulty in diagnosing cerebral embolism in assessing the symptoms and cause of death of patients with fractures. At necropsy the brain is carefully examined for petechiæ in the white matter, and rapid frozen sections of brain and kidney for lipid are now often made; by this means 8 other cases of unsuspected cerebral fat-embolism causing or contributing to death have been revealed in this hospital during the past year. It is clear that some of the unsuspected cases with histological systemic (and cerebral) embolism are clinically important and may be fulminating cases (see later), whilst others seem to be subclinical.

Systemic embolism varies considerably in its severity and clinical picture, and may be classified into (1) fulminating cases, (2) the classical or full syndrome, and (3) a number of incomplete or partial syndromes.

Fulminating Cases

The injuries are generally severe and multiple fractures are usually present; these patients die one to three days after injury, even though hæmorrhage and oligæmia may have been adequately combated by early and efficient transfusion. As noted above, these cases are usually recognised by retrospective correlation of unexplained cerebral symptoms with cerebral fat-emboli at necropsy.

A common story is that the patient was initially conscious after injury but became stuporose and then comatose, sometimes within a few hours and generally within one or two days. The onset of coma may be masked by general anæsthesia for surgery, but consciousness does not return. There may be weakness of one or more limbs or occasionally hemiparesis. Epileptiform or choreoathetoid movements—focal, unilateral, or generalised—may occur. Collapse during resuscitation or failure to maintain benefit after blood-transfusion may dominate the picture; hence fulminating cerebral embolism may be one of the causes of " irreversible shock " (Sevitt 1958).

Rapid onset of serious symptoms may also occur in patients with single fractures:

Example.—A man of 25 was admitted with a compound fracture of the leg. His general condition was satisfactory, and he was conscious. Sixteen hours later he had a headache, and he vomited and became drowsy. Weakness of the right arm and leg was noted. Extradural hæmorrhage was suspected and burr holes were made in the skull, but no hæmorrhage was seen. He remained unconscious and died thirty-two hours after injury. Necropsy showed petechiæ in the cerebral and pontine white matter, and in parts of the cortex, and frozen sections of the brain, kidney, and other organs revealed fat-emboli.

Fulminating fat-embolism is of course difficult to diagnose. Clinically death may be attributed to the delayed effect of a head injury (there is added difficulty if the patient was concussed), to an anæsthetic misadventure, or to other causes of post-traumatic coma. A petechial eruption is absent or very sparse, and easily overlooked presumably because the patient dies before it normally appears. Even a few characteristically located skin petechiæ may be of great help in differential diagnosis; renal biopsy for glomerular embolism can also be helpful (see below).

At necropsy the petechial hæmorrhages in the white matter of the cerebrum may be few or ill defined if death has occurred within a day or so of injury; often the white matter only shows a somewhat excessive vascular punctation without definite hæmorrhagic spots. Frozen sections of the brain stained for lipid are essential for diagnosis, and should form a routine part of the histology of all subjects with fractures reaching necropsy.

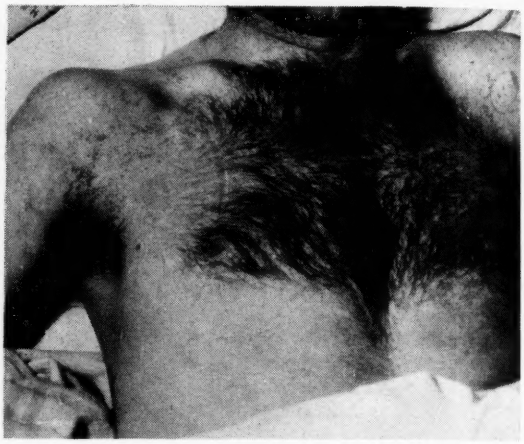

Fig. 1—The petechial rash of fat-embolism characteristically located in front of the upper part of the chest and shoulders.

The Classical Syndrome

This well-known picture is characterised by major cerebral and neurological effects, respiratory symptoms, pyrexia, tachycardia, and a characteristic petechial eruption of much diagnostic importance (fig. 1).

The first symptoms generally develop within twenty-four hours of the accident, and not about the third day, as is commonly stated. In the records of 75 cases, some published and others personally observed, symptoms were present in 23% within twelve hours of injury, in 60% within twenty-four hours, in 80% within thirty-six hours, and in over 90% within forty-eight hours. The early symptoms are important because their significance may be overshadowed by other effects of injury; recognition is often delayed until the disorder of consciousness is serious, or the rash attracts the clinician's attention.

The *onset* is often sudden. A pyrexia of 102–103° F or even higher, and a tachycardia of 100–120 per minute are usual. Cerebral and respiratory symptoms develop simultaneously or at different times, and one or other may predominate. Restlessness, delirium, and insomnia often precede or accompany mental confusion or stupor which may later deepen into coma. Other possible neurological symptoms include incontinence, convulsions, disturbances or pupillary reflexes, spasticity, increase or loss of deep reflexes, and even paralysis of a limb or muscle-groups.

Respiratory distress is manifest by dyspnœa, polypnœa, possibly cyanosis, and tightness in the chest. Moist sounds in the lungs, cough, and sputum may be present. The respiratory effects cannot be due to the pulmonary emboli (see below), and they are presumably neurogenic in origin from cerebral emboli. Neurogenic pulmonary œdema is now well recognised, whilst acute respiratory symptoms not uncommonly complicate acute cerebral disease, such as spontaneous and traumatic cerebral hæmorrhage, and brain operations (see Cameron 1948). Thus respiratory effects from cerebral emboli are not surprising.

The *blood-pressure* does not fall unless oligæmia was untreated or until terminal cardiac failure supervenes. Thus the so-called " cardiac syndrome " is a myth, and was probably due to the accompanying effects of untreated hæmorrhage. The jugular veins are rarely distended even when blood-transfusion is in progress.

The *petechial eruption* is preceded by other symptoms, and it usually develops on the second or third day after injury (fig. 1). It appears on the front of the shoulders, the root of

the neck, and the upper parts of the chest; it may be restricted or extend over the arms, upper abdomen, and even the thighs. The petechiæ are often fine red spots, though sometimes they are relatively coarse. They appear in crops over a day or two, each crop fading within a few days. The uninitiated may mistake the combination of pyrexia and a petechial eruption for septicæmia.

The mortality in this type is likely to be high because of the coma, but it can be reduced by modern treatment for comatose patients. In recent years heparin therapy has had its advocates, but its effectiveness remains unproved. There was 1 death among the 4 classically complete cases which I investigated.

Incomplete and Partial Syndromes

In most clinically diagnosable cases some of the classical symptoms are absent. The course is usually less severe than in the classical picture, and many cases are mild. 16 of the 20 cases of systemic embolism which I studied showed an incomplete or partial clinical picture; all survived. Primary diagnosis was made from the characteristic petechial rash; affected skin from the shoulder was biopsied in 10 cases, and the diagnosis was confirmed by finding embolic fat globules in dermal capillaries (fig. 2).

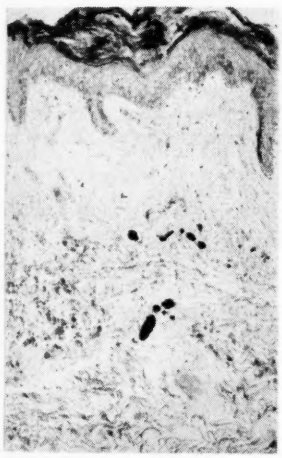

Fig. 2—Biopsy of skin from the rash.
Note the embolic fat globules in dermal capillaries, and the focus of hæmorrhage nearby. (Frozen section; Sudan red × 110.)

These cases subdivide into 3 groups:

Those without respiratory symptoms, but with cerebral and sometimes neurological symptoms, pyrexia, tachycardia, and a petechial rash (5 cases).

The cerebral effects were severe in 1 patient (stupor, semicoma, incontinence, and temporary paresis of one arm), but in the others they were relatively mild (mental confusion in all 4 and retrograde amnesia in 1). The patient with amnesia also had respiratory difficulty, but this was attributed to multiple rib fractures.

Example.—A man of 54 fractured his right tibia and fibula, and a plaster cast was applied the same day. Next day, his temperature rose to 101°F. The following night he became semicomatose and was aroused with difficulty; temperature 102°F, pulse 96 per min. He became incontinent of urine and his right arm was noticeably weaker than the left. A stroke was suspected, but by the third day a petechial rash appeared on his shoulders and later spread to the chest. A skin biopsy specimen revealed fat emboli in the dermal capillaries. The patient remained stuporose for a few days, with some spasticity of the limbs, but by the eleventh day after injury he had recovered except for occasional incontinence. Respiratory effects were conspicuously absent.

Those without cerebral symptoms, but with respiratory distress or polypnœa as well as pyrexia, tachycardia, and a petechial rash (4 cases).

Example.—A man aged 41 was run into by a car and knocked out for a few seconds. His knee was swollen from a fissure fracture of the upper end of the tibia involving the joint; the leg was splinted. Next evening his temperature rose to 103°F, pulse-rate 120 per min., and he complained of headache. There was slight dyspnœa. A petechial rash in front of the chest and shoulders established the diagnosis, which was confirmed by skin biopsy and by the finding of fat globules in the urine. Next day he became very dyspnœic (respiratory-rate 60–70 per min.), and an oxygen tent was necessary. Radiographs showed a diffuse patchy shadowing of both lung fields. His temperature was now 104°F, and the rash had spread to the front of the abdomen and thighs. He was mentally clear; there were no cerebral symptoms or neurological signs, and he was not incontinent.

Those without significant cerebral or respiratory symptoms (7 cases). Diagnosis was based on the characteristic petechial rash; in 2 cases skin biopsy was done and confirmed the diagnosis. Pyrexia and tachycardia were variable.

Example.—A man of 20 sustained a compound comminuted fracture of the tibia. This was plated next day under general anæsthesia, and he was transfused with 4 bottles of blood. The following day his temperature was 100–101°F, and a petechial rash appeared over the front of the chest and arms. He was otherwise well except for some lower abdominal pain; there was no cough, dyspnœa, or mental symptoms. Fat-embolism would never have been considered but for the rash.

Systemic Embolism Without Petechial Rash

Without the rash the possibility of fat-embolism is rarely suspected or is on much less certain ground. Some patients die from embolism or from other causes, and, no doubt, many survive. Several cases other than the fulminating ones, with cerebral fat-embolism at necropsy, had obscure cerebral symptoms during life but had no rash, whilst others were without significant cerebral or respiratory symptoms. No doubt many survive with or without cerebral effects of embolism, and in some the only symptoms are pyrexia or tachycardia.

Aids to diagnosis would be most helpful in the severe cases without a rash. Unfortunately no reliable simple test has been developed, and diagnosis still largely depends on clinical acumen. The finding of fat in the sputum is common, but at most indicates pulmonary embolism. Examination of the urine for fat is unreliable. Several samples of urine were examined from most of the present cases but in only 2 was fat detected. This contrasts with the report of Musselman et al. (1952), who found urinary

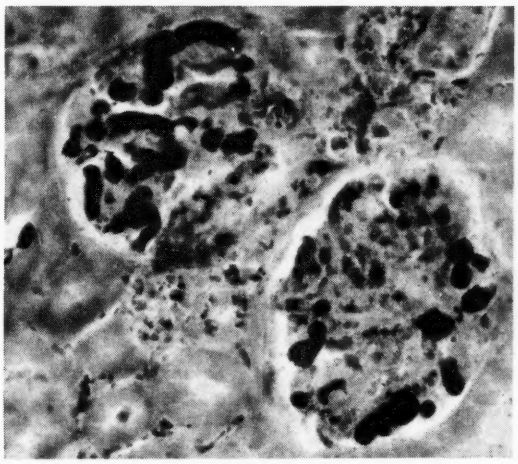

Fig. 3—A heavy degree of glomerular fat-embolism.
(Frozen section; Sudan red × 105.)

fat in over 50% of 109 injured patients (and in 12% of 50 uninjured patients), but they examined 15 consecutive twenty-four-hour specimens of urine from each patient. Of course negative results may be due to incomplete emptying of the bladder since fat floats in urine. Microscopy of the plasma for globules of fat has been described (Peltier 1954, 1956) but the test is still in the experimental stage, and further work is needed to relate the pathological and clinical evidence of embolism.

Renal Biopsy

Needle biopsy of the kidney, which can be of value, should be considered in special cases—e.g., obscure post-traumatic coma. I have used it when craniotomy was being considered for possible intracranial hæmorrhage. The finding of glomerular fat-emboli is proof of systemic embolism (fig. 3) and, by inference, cerebral embolism. Using the Vim-Silverman needle the biopsy is not difficult and is relatively safe. Rapid frozen sections should be stained for lipid; or, if this cannot be done quickly, part of the thin core of the renal tissue obtained should be flattened between glass slides, and then stained for fat with a fat-soluble dye. Unequivocal fat-emboli in glomerular capillaries are easy to recognise under the microscope.

Discussion

Although pulmonary fat-embolism is very common after injury and almost universal after fracture of marrow bones, evidence from clinical, pathological, and experimental sources strongly indicates that it rarely, if ever, causes significant symptoms or produces pathological changes in the lungs. This presumably reflects the large reserves of the lungs and the fluid nature of the emboli. Trapping of the emboli may be considered physiological rather than pathological; and it is also protective in that fewer or no emboli will then reach the systemic circulation. On the other hand, systemic embolism can be clinically important, but only a fraction of those with pulmonary emboli at necropsy have systemic emboli. The frequency of systemic embolism at necropsy is higher when pulmonary embolism is relatively gross, and when many marrow bones are fractured. This is in apparent contradiction to ordinary clinical experience, because most cases of systemic embolism are diagnosed in patients with a fracture of one or at most two long bones, usually the tibia or femur. But the discrepancy is more apparent than real, because a necropsy series will naturally include many severely injured patients with multiple fractures (in whom the likelihood of systemic embolism is high), whilst the clinically diagnosed cases are found among a much larger group of injured survivors, most of whom have less severe injuries and fewer fractures.

The prognosis of clinical embolism is particularly affected by the presence and severity of cerebral symptoms. The mortality of those in coma is relatively high, whereas it is low in those with mild cerebral effects or without cerebral symptoms. The greater frequency of cases of mild or moderate severity, of which a variable proportion go undiagnosed, is responsible for the variable reports of prognosis. This point is important if potential remedies are to be properly assessed; the mild and less severe cases will recover with or without treatment, but the group of comatose patients has a relatively high mortality.

Necropsy evidence also indicates that mild and even subclinical cases of systemic embolism are not infrequent. Some of the cases discovered at necropsy had apparently never developed symptoms referable to the emboli, and had died of other causes. Thus some patients seem to tolerate some embolic fat in the brain, whilst in others various degrees of cerebral disorder are produced. Histologically, scantiness of cerebral emboli is related to absence of cerebral effects; but at necropsy, in a series of which none was clinically suspected of embolism, it can be difficult to pick out histologically the symptom-producing from the subclinical emboli.

Summary

An analysis of the significance and classification of fat embolism is based on material from 100 cases dying after injury, and from 17 clinically diagnosed patients.

Histological evidence shows that pulmonary fat-embolism is very common after injury but rarely causes symptoms or produces abnormal changes in the lungs. Systemic (including cerebral) embolism varies considerably in its severity and symptoms. Prognosis mainly depends on the presence of coma.

Systemic embolism is divisible into (1) fulminating cases, dying in coma within a day or two of injury; (2) the classical syndrome of cerebral and neurological symptoms, with respiratory distress, pyrexia, tachycardia, and a characteristic petechial rash, and carrying a high mortality; and (3) incomplete and partial syndromes, in which cerebral or respiratory effects, or both, are absent, and in which mortality is low.

The rash is of importance in diagnosis, and cases without a rash are difficult to diagnose. Needle biopsy of the kidney, to demonstrate glomerular fat-embolism, is recommended in special cases—e.g., obscure post-traumatic coma.

My thanks are due to various clinical colleagues for their cooperation in studying the patients, and to Mr. R. Gill and Miss V. Montague-Smith, of the photographic department, for the illustrations.

REFERENCES

Armin, J., Grant, R. T. (1951) *Clin. Sci.* **10**, 441.
Cameron, G. R. (1948) *Brit. med. J.* i, 965.
Cohnheim, J. (1889) Lectures in General Pathology. London.
Emson, H. (1958) *J. clin. Path.* **11**, 28.
Gold E., Loeffler, E. (1923) *Z. ges. exp. Med.* **38**, 155.
Grant, R. T., Reeve, E. B. (1951) *Spec. Rep. Ser. med. Res. Coun., Lond.* no. 277.
Green, H. N., Stoner, H. B. (1950) Biological Action of the Adenine Nucleotides. London.
Harman, J. W., Ragaz, F. J. (1950) *Amer. J. Path.* **26**, 551.
Harris, R. J., Perrett, T. S., Maclachlin, A. (1939) *Ann. Surg.* **110**, 1095.
Lehman, E. P., Moore, R. M, (1927) *Arch. Surg., Chicago*, **14**, 621.
Musselman, M. M., Glas, W. W., Grekin, T. D. (1952) *ibid.* **65**, 551.
Peltier, L. F. (1954) *Surgery*, **36**, 198.
— (1956) *J. Bone Jt Surg.* **38A**, 835.
Scriba, J. (1880) *Dtsch. Z. Chir.* **12**, 118.
Scuderi, C. S. (1941) *Surg. Gynec. Obstet.* **72**, 732.
Scully, R. E. (1956) *Amer. J. Path.* **32**, 379.
Sevitt, S. (1957) *in* Proceedings of the Pathological Society of Great Britain and Ireland, 1956. (Abstracted in *Ned. Tijdschr. Geneesk.* p. 1522.)
— (1958) *Med. Pr.* **239**, 403.
— (1959) *in* Modern Trends in Accident Surgery and Medicine (edited by R. Clarke, F. G. Badger, and S. Sevitt). London.
Wilson, J. V. (1946) Pathology of Traumatic Injury. Edinburgh.
Whiteley, J. H. (1954) *J. Path. Bact.* **67**, 521.

"... The lack of general awareness that as a community we are a good deal less than reasonably efficient in the social sense is extremely disturbing. We are concerned at the loss of 3,500,000 working days through industrial disputes, but a loss of 28,000,000 working days through various forms of mental illness seems to cause no disquiet. We are appalled by the fatal road accident rate, but the equal incidence of suicide is the concern of no Minister."—G. C. JOHNSON. *Listener*, Sept. 22, 1960, p. 451.

NATURE OF ESSENTIAL HYPERTENSION

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THE notion that high blood-pressure without evident cause in middle age is merely the tail end of the distribution of blood-pressure in the population is an interesting and important one (Hamilton et al. 1954b, Pickering 1955, Oldham et al. 1960). However, to our mind there is little evidence in favour of it and much against it.

"Low" or "Physiological" Levels of Blood-pressure

It seems likely that the level of blood-pressure in healthy people *is* a graded characteristic—i.e., it is continuously distributed, probably in a symmetrical, "normal" way. It is also likely that inheritance plays a small part in setting the pressure of an individual and that the nature of the inheritance is multifactorial. The evidence for this is provided by the surveys of Miall and Oldham (1955, 1958) on random samples of the population; these surveys showed that there is a highly significant relationship between casual pressures in subjects and in their first-degree relatives. This is expressed by regression coefficients of 0·22 for systolic and 0·18 for diastolic pressures, which mean that, for every 10 mm. Hg that pressures of subjects are above or below the average, the mean pressures of their relatives will be approximately 2 mm. above or below average respectively. These results, being representative of a total population, are based predominantly on subjects with low, as opposed to high, pressures: 24 in a total of 612 subjects had diastolic pressures greater than 100 mm. Hg; and of these only 12 had pressures higher than 110 mm. Hg.

Are There Two "Populations"?

The crucial question is whether people having high blood-pressure without evident cause, particularly in middle age (essential hypertension), are merely the tail end of the physiological or normal distribution of pressure, or whether they can be shown to form a qualitatively distinct group—a separate "population".

There is abundant evidence that no clear-cut dividing-line between physiological levels and essential hypertension can be found. If there were such a division, there could be no controversy. Distributions of pressures in the population are thus "continuous", in the sense that there is no break between low and high pressures. However, as discussed earlier (Morrison and Morris 1959), it has been shown (Harris and Smith 1949) that such distributions by no means preclude the presence of two or more distinct "populations". Platt (1960) has illustrated how a combined frequency distribution of two distinct but overlapping distributions can produce a "continuous" curve. The examination of general population samples, therefore, is unlikely by itself to determine whether these are homogeneous or include overlapping distributions that represent more than one "population". E t the absence of a dividing-line in such distributions is not an argument for the theory of continuous variation—it is simply negative. What it does mean is that some other way of classifying individuals is necessary if it is suspected that two separate populations are present. Similar problems have been met in biochemical genetics (Harris et al. 1960).

Evidence for Two Populations

One way of testing the hypothesis that there are in fact two distributions is to examine relatives of hypertensives. According to the single gene hypothesis, they should segregate into hypertensives and normotensives in roughly equal proportions; with such a high proportion of hypertensives the distribution should indicate the presence of two populations by being bimodal. Platt (1959) carried out such a test by plotting the pressures of middle-aged sibs of middle-aged hypertensives from the data of Hamilton et al. (1954b) and of Sobye (1948). In both sets of data the sibs showed a bimodal distribution of pressures—though it does appear that observer bias helped to produce it in Sobye's. The systolic pressures of middle-aged sibs of hypertensives in the data of Weitz (1923) also show bimodality. The only study which does not clearly produce a bimodal distribution among sibs of hypertensives is that of Oldham et al. (1960).*

We used a different method of analysis with data on busmen. Whatever else might be in question, two things are widely accepted about essential hypertension: first, that it shortens the expectation of life, and, second, that a hereditary factor of some kind is concerned in its development. If therefore we divide a given population into those whose parent(s) die in middle age and those whose parents live to old age, we shall have made use of these factors, heredity and premature death, to obtain one group containing more individuals with high blood-pressure and one containing less. If the parents who die prematurely include a large proportion with essential hypertension, there should then be a large enough proportion of hypertensive sons to indicate segregation into normotensives and hypertensives by the appearance of bimodality in the distribution of blood-pressure among the sons. In our investigation of busmen this was a long shot—but it came off. The drivers whose parent(s) died in middle age showed a bimodal distribution of blood-pressure, whilst the remainder did not.

Thus in groups selected by the inheritance factor, bimodality—signifying the presence of two populations, one hypertensive and the other normotensive—has been found every time it has been looked for, with a single possible exception. Attempts to explain away these findings (Pickering 1959a, Oldham et al. 1960) are understandable but unhelpful.

Objections (Oldham et al. 1960) have been levelled at our method of selective analysis on the ground that hypertension is commoner among those who die over 65 than among those who die before this age. Figures were given in support of this objection showing (1) that deaths from cardiovascular and cerebrovascular diseases "commonly associated with hypertension" form a higher proportion of all deaths after 65 than before this age, and (2) that casual systolic pressures over 160 mm. Hg are common over the age of 65 and increase steadily in frequency as age advances. The first objection is beside the point. We are comparing groups where, on the one hand, a parent died in middle age and, on the other hand, both parents survived to at least 65. Data from the national necropsy survey (Morris and Crawford 1958) show that the proportion with essential hypertension at necropsy in middle-aged men (45–64) was as follows: in deaths from injuries, infections,

* Oldham et al. quote data from the "truly random" samples of Miall and Oldham (1955, 1958). The figures are curious, however, since they include "84 sibs aged 45–59 derived from propositi aged 45–59 with diastolic pressures of 100 mm. Hg or above". Yet there are only 15 such propositi.

cancer, &c., 11%; in deaths from ischæmic heart-disease, 35%; in deaths from cerebrovascular disease, 65%; and in deaths from other remaining conditions, 36%. These are figures of severe hypertension, nearly all of fixed diastolic hypertension that produced left ventricular hypertrophy. Figures of blood-pressure in old age are scanty, but the surveys of Hamilton et al. (1954a) and Miall and Oldham (1958) show that, of men surviving to ages 65–69, only 8% had diastolic pressures higher than 110 mm. Hg and only 2% had pressures above 120 mm. The prevalence of high *systolic* pressures in old age can be safely used as an indicator only of the prevalence of arteriosclerotic rigidity of large arteries, not of the prevalence of essential hypertension.

In general, it may be said that if premature death of parents among these busmen is not an indicator of the inheritance factor in essential hypertension it is an indicator of something even more interesting. We have an open mind on this and are working on it.

We do not follow the figures of Oldham et al. on the age at death of parents of hypertensives. If these refer to the parents of middle-aged male hypertensives they certainly contradict ours. We hope to produce further information on this question.

Resemblance Between Relatives

If the theory of continuous variation and multifactorial inheritance applies to "essential hypertension"—as it almost certainly does to physiological levels of pressure—the degree of resemblance between relatives will be the same at high levels of pressures as it is at low. That this is the case is, in fact, repeatedly claimed (Pickering 1959a and b, Miall and Oldham 1955, 1958, Oldham et al. 1960). The resemblance, using "sex and age-adjusted scores",† is said to be measured by a regression of a little over 0·2 among those with high pressures, which is very similar to the regressions calculated by Miall and Oldham for those with low pressures. However, this figure of a little over 0·2 is usually derived from calculations that are quite irrelevant to the question of the multifactorial inheritance of a graded character. When the regression coefficients for hypertensives and their relatives are calculated correctly, like those of Miall and Oldham (and of Galton), they are 0·05 for systolic and 0·06 for diastolic scores. These regressions are not significant. (Of course, the scores of relatives are on average raised as would be expected on any genetic hypothesis.) Fig. 1 shows the diastolic scores of subjects and the corresponding average scores of their relatives (adapted from table VI of Hamilton et al. 1954b). The first and last points manifestly do not "belong" with the others; but their exclusion makes little difference to the regressions. Moreover, what little interest there is in these regressions of 0·05 and 0·06 depends heavily on subjects with diastolic pressures just over 100 mm. Hg—i.e., just the group most likely to include subjects from the high end of the physiological distribution. If these subjects and their relatives are excluded, the regressions become rather less than 0·04 for both systolic and diastolic pressures; these regressions are significantly different from those of Miall and Oldham (1958). Thus the data indicate that at high levels of pressure there is little if any graded relationship between the height of the pressure in individuals and in their first-degree relatives.

† We think that the use of such scores and the assumptions they involve are quite unwarranted in the present state of knowledge of the relationship of sex and age to blood-pressure and essential hypertension. However, even using these scores we demonstrate below that inheritance appears to be different at high pressures from that found at low.

Another defect of the studies of Hamilton et al. (1954b) and of those of Miall and Oldham (1955, 1958) is that little attempt was made to distinguish family-environmental similarity that might affect the blood-pressure of close relatives from strictly genetic factors.

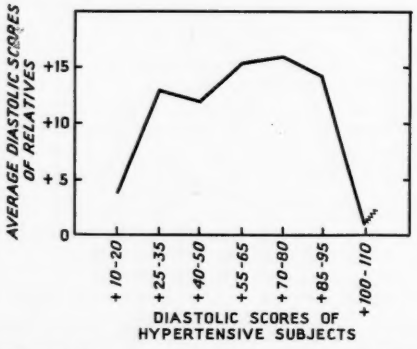
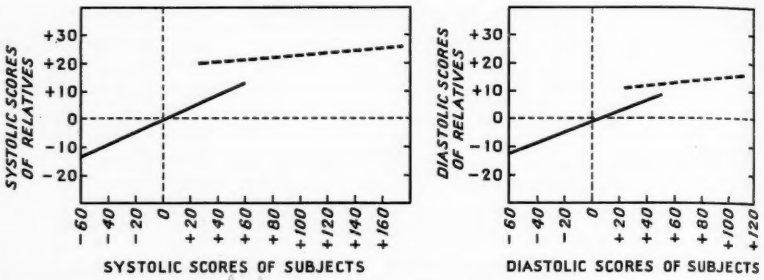


Fig. 1—Diastolic "sex and age-adjusted scores" of subjects with corresponding average scores of their relatives (adapted from table VI, Hamilton et al. 1954b).



Regression lines at low pressure levels (Miall and Oldham 1958).

Regression lines at high (subjects with diastolic pressures above 110 mm. Hg) pressure levels (Hamilton et al. 1954b).

Fig. 2—Regression lines of relatives' scores on subjects' scores for subjects with low pressures and subjects with high.

Fig. 2 illustrates the regression lines of Hamilton et al. for a population with high pressures and those of Miall and Oldham for a population overwhelmingly with low pressures. There appears to be a clear break in continuity—evidence that the mode of inheritance at high levels differs from that at low, again indicating that there are two qualitatively different populations.

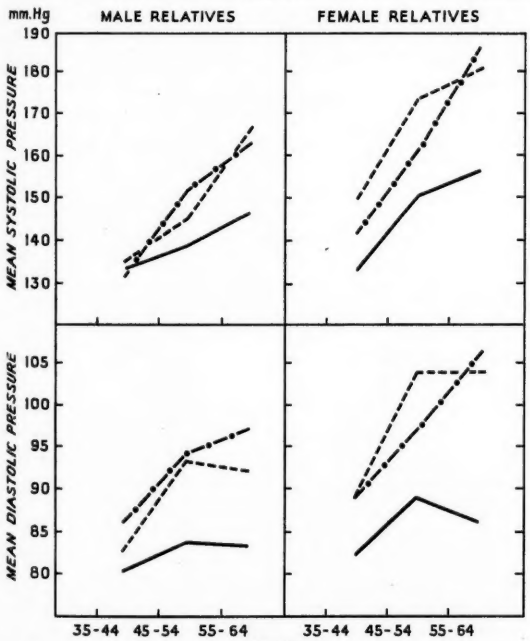
Rise of Blood-pressure in Middle Age

The next test of the hypothesis that there are two "populations" is to consider the common finding that average blood-pressures of population samples increase with age (e.g., Buchan et al. 1960). Is this due to a general increase among individuals as they pass through middle age, or is it largely due to the emergence of a special population with a special disease—those developing essential hypertension? Until relatives of hypertensives and of others can be followed *as individuals* through middle age it will be impossible to give a definite answer. But

group comparisons can give a strong hint. Fig. 3 compares the rise of average pressures among relatives of normotensives and relatives of hypertensives. We have used data of relatives of normotensives of all ages and, following Platt (1959), relatives of middle-aged hypertensives. The relatives of hypertensives, as expected on the hypothesis that a large proportion of them will become hypertensive during middle age, show a significantly greater increase with age than the relatives of normotensives (see accompanying table). If they form any sizeable fraction of the population, hypertensives and their families must surely contribute very disproportionately to the rise of average blood-pressure that is found during middle age. In normotensive families, diastolic pressures scarcely rise at all; but women in such families do show a pronounced rise of *systolic* pressures. Since numbers are very small, Sobye's data are also shown on the figure—they behave very like those of Hamilton et al.

Bus drivers also show that the rise in average pressures is mainly seen in hypertensive families.

Among men with a parent who had died early we found indications of a bimodal distribution of systolic pressures at ages 45–54, and at 55–60 a clearly bimodal one with normotensive and hypertensive peaks. In both age-groups the distribution of pressure among those whose parents lived to old age was unimodal. The peaks of the bimodal distributions among sons with a parent who died early corresponded closely at the two ages. The rise of blood-pressure during middle age among drivers was almost confined to men with a parent who died early; and it was produced by the much higher proportion of men found in the second hypertensive peak of the bimodal distribution at 55–60 than at 45–54 (Morrison and Morris 1959).



Relatives of normotensive subjects (Hamilton et al. 1954b).

Relatives of middle-aged hypertensive subjects (Hamilton et al. 1954b).

Relatives of middle-aged hypertensive subjects (Sobye 1948).

Fig. 3—Rise of mean pressures with age among relatives of middle-aged (45–64) hypertensive subjects and among relatives of normotensive subjects.

RATE OF RISE OF PRESSURE WITH AGE IN RELATIVES OF HYPERTENSIVES AND RELATIVES OF NORMOTENSIVES (mm. Hg PER 10 YEARS OF AGE*)

Pressure	Sex	Relatives aged 35–64 of middle-aged † hypertensive subjects	Relatives aged 35–64 of normotensive subjects
Systolic	M	16·7 (58 men)	7·3 (98 men)
	F	17·7 (98 women)	11·4 (122 women)
Diastolic ..	M	5·1	1·5
	F	8·5	2·9

Combining probabilities in the two sexes, the differences between relatives of hypertensives and relatives of normotensives are significant ($P<0.05$) for both systolic and diastolic pressures.
* Data of Hamilton et al. 1954b.
† Middle-aged = 45–64 years.

Other analyses of pressures are now being made—e.g., following Perera (1960). All this is suggestive evidence once more that there are two populations.‡

Keen and Rose (1959) criticised our analyses by suggesting that parents who died prematurely include two groups, one with low blood-pressure and the other with high; that each of these is producing in the sons a unimodal distribution, and that when these are amalgamated an artefact bimodal curve in the sons is the result. If this criticism is valid, the proportion of hypertensive deaths among the parents of sons aged 45–54 must have been much smaller than that among parents of sons aged 55–60 since the proportion of hypertensive drivers is much lower at 45–54 than at 55–60. Our data on cause of death are meagre, but there is no evidence whatever of such a difference. It may be added that fig. 1 of Keen and Rose ignores the age factor and contains errors of plotting and smoothing.

Conclusion

There does not seem to be any evidence on which to base a New Theory of essential hypertension. On the contrary, what evidence there is (and it is far from perfect) suggests that the common high blood-pressure without evident cause in middle age is qualitatively different from normal blood-pressure. Moreover, these cases of essential hypertension behave so homogeneously that it is reasonable to postulate they consist predominantly of a specific disease entity.

Future Work

One of the main conclusions of the Symposium on the Pathogenesis of Essential Hypertension (1960) held in Prague was that more knowledge about the natural history of the disease is urgently needed. In seeking this knowledge, there is clearly a place for epidemiological studies of complete populations (Morris 1957), and these studies must be prospective. They should be on an adequate scale: none of the studies we have been quoting is large enough satisfactorily to settle the issues that have been raised. For example, such studies should include large enough numbers of middle-aged subjects and their middle-aged relatives to allow separate analysis of actual pressures in the two sexes, thus obviating any need for "sex and age-adjusted scores"; and the studies should be designed to avoid observer bias.

One difficulty of population studies is what measure of blood-pressure to use. Is the casual pressure a meaningful indicator of average pressure during daily life, or should some attempt be made to measure basal pressures (Smirk 1957)? Furthermore, in cases of intermittent

‡ The demonstration by Oldham et al. that, after following up a large number of people for four years, two populations in respect of the rise of pressure with age were not revealed, does not help. Some kind of genetic analysis seems to be necessary to disclose these two populations.

corrections work p. 1138

hypertension, what pressure is to be used as the index for family studies? Much work is needed on these elementary questions. In our studies of busmen (Kagan 1960) several pressures were taken during the course of a $1^1/_2$ hour examination, and these are now being analysed in relation to the casual pressure.

There is much scope for international studies of blood-pressure. Oldham et al. have pointed out the similarity between mean pressure values in Britain, in farm workers in the U.S.A., and in tea workers in Assam. It is even more interesting that notable differences in mean values have been found between British studies and others. For example, male Fijians and Indians in Fiji (Lovell et al. 1960) and Africans in East Africa (Williams 1941) show little if any rise of pressure during middle age, while some Indians in India show only slight increases (Chopra et al. 1942).

There is one particularly important area for study—the zone of overlap between the high end of the normal distribution and the low end of essential hypertension. We have found, in two independent sets of data, a suggestion (numbers are too small to say more) that there may be a different relationship between systolic and diastolic pressures among men from "hypertensive" families and men from "normotensive" families in this zone of overlap. Other analyses of the relationships are now being made. Until this zone is clarified there will continue to be many definitions of "hypertension". But surely this is unimportant—difficulty in defining it does not mean that there is no specific disease.

We are grateful again to our friends and colleagues for much help. In particular, we wish to thank Prof. Harry Harris and Prof. Clifford Wilson.

REFERENCES

Buchan, T. W., Henderson, W. K., Walker, D. E., Symington, J., McNeil, I. H. (1960) *Hlth Bull., Edinb.* **18**, 1.
Chopra, R. N., Chopra, G. S., Chopra, I. C. (1942) *Indian med. Gaz.* **77**, 21.
Hamilton, M., Pickering, G. W., Roberts, J. A. F., Sowry, G. S. C. (1954a) *Clin. Sci.* **13**, 11.
— — — — (1954b) *ibid.* p. 273.
Harris, H., Whittaker, M., Lehmann, H., Silk, E. (1960) *Acta genet.* **10**, 1.
— Smith, C. A. B. (1949) *Ann. Eugen.* **14**, 309
Kagan, A. R. (1960) In preparation.
Keen, H., Rose, G. (1959) *Lancet*, ii, 1028.
Lovell, R. R. H., Maddocks, I., Rogerson, G. W. (1960) *Aust. Ann. Med.* **9**, 4.
Miall, W. E., Oldham, P. D. (1955) *Clin. Sci.* **14**, 459.
— — (1958) *ibid.* **17**, 409.
Morris, J. N. (1957) Uses of Epidemiology. Edinburgh.
— Crawford, M. D. (1958) *Brit. med. J.* ii, 1485.
Morrison, S. L., Morris, J. N. (1959) *Lancet*, ii, 864.
Oldham, P. D., Pickering, G. W., Roberts, J. A. F., Sowry, G. S. C. (1960) *ibid.* i, 1085.
Perera, G. A. (1960) *ibid.* ii, 153.
Pickering, G. W. (1955) High Blood Pressure, London.
— (1959a) *Lancet*, ii, 1027.
— (1959b) *in* Ciba Foundation Symposium on Significant Trends in Medical Research (edited by G. E. W. Wolstenholme, C. M. O'Connor, and M. O'Connor). London.
Platt, R. (1959) *Lancet*, ii, 55.
— (1960) *ibid.* i, 1189.
Smirk, F. H. (1957) High Arterial Pressure. Oxford.
Sobye, P. (1948) Heredity in Essential Hypertension and Nephrosclerosis. Copenhagen.
Symposium on the Pathogenesis of Essential Hypertension, Prague (1960) Proceedings (in the press).
Weitz, W. (1923) *Z. klin. Med.* **96**, 151.
Williams, A. W. (1941) *E. Afr. med. J.* **18**, 109.

"... The widening gap between the general practitioner and the hospital specialist has received much publicity in lay as well as medical circles, but a second fissure is opening—one which bids to be just as wide and just as lamentable in its consequences. I refer to the divorce between the bedside clinician and the clinical scientist ... There is no basis in fact for division of our profession into an intelligentsia of investigators and a peasantry of practitioners. Research and the bedside practice of medicine indeed demand different talents, but each requires for success mental endowments of comparable quality."—Prof. I. G. W. HILL, *Scot. med. J.* 1960, **5**, 397.

PULMONARY EMBOLISM
A STUDY OF LATE PROGNOSIS

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A PULMONARY embolus may cause rapid death. Those patients who survive the initial catastrophe are usually expected to recover completely, though it is recognised that very occasionally pulmonary hypertension ensues (Magidson and Jacobson 1955, Wood 1956). A clinical impression that much disability often persists led to a follow-up study of patients with pulmonary embolism; no investigation of late prognosis after pulmonary embolism has been reported.

Clinical Material

All patients diagnosed as having pulmonary embolism at the Central Middlesex Hospital in the three years 1957–59 were reviewed. There were 136 patients (75 women and 61 men) in whom the diagnosis was satisfactorily substantiated. 65 died immediately or within a few hours.

Of the 71 survivors, 58 were seen personally. 4 for reasons such as age or distance were not seen, but information about their progress was recorded in outpatient notes; and follow-up information was also available about 6 who had subsequently died. Full information was not obtained about 3 of the 71 patients: 1 had died, 1 had moved, and 1 refused to attend hospital.

The follow-up, then, concerns 68 patients—33 women and 35 men. The mean interval between the pulmonary embolism (or the first incident if recurrent) and the follow-up was 17·6 months.

The average age of the 136 patients was 63·6 years. In other series there has been a similar high average age; Barnes (1937) for instance, found that 93% of his patients were over 40 years of age.

Embolic Episodes

Secondary Infection

Secondary staphylococcal infection occurred in 6 of the patients; 2 of these, with resistant strains, were extremely ill with abscess formation (Elliott, Gresham, and Phear 1960) but recovered although left with some disability. In a further patient with a severe chest infection, who died despite tetracycline treatment, a resistant staphylococcus was probably present though no sputum culture was obtained. In 1 patient pyopneumothorax due to *Clostridium welchii* developed, and in 2 patients a pneumococcal infection.

Arrhythmia

At the time of the embolism 1 patient had transient auricular fibrillation and another transient auricular flutter; both recovered completely. In 8 patients auricular fibrillation developed at the time of the embolism and persisted.

Recurrent Embolism

12 patients had recurrent embolism. The average interval between emboli was 2·6 years in the 6 patients with varicose veins, and 1·1 years in the remaining 6 patients with deep venous thrombosis.

Late Prognosis

Of the 68 survivors, reviewed after an average interval of 17·6 months, 42 had recovered completely after the embolism. 7 reported slight dyspnœa; 9 complained of moderate dyspnœa, and 1 of these had persistent auricular fibrillation. 10 patients were severely disabled, and it is these patients I wish particularly to describe.

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Of the 10 patients (6 women and 4 men) with severe persisting symptoms 7 had had clinically recurrent embolism. Before the onset of embolism all 10 had been well and active for their age. In only 1, a man with symptomless mitral incompetence, was there known previous heart or lung disease. Afterwards, 3 were in gross heart-failure and died, while in the rest heart-failure was controlled with varying success. Exertional dyspnœa and fatigue were notable. The average age of these 10 patients (67·0 years) was higher than that of the 9 patients with moderate dyspnœa (64·3 years) and of the completely recovered patients (52·6 years).

Of the 10 patients, 2 presented a clear picture of pulmonary hypertension and right ventricular failure:

Case 1.—A West Indian woman, aged 25, was delivered normally of a healthy boy on Feb. 2, 1958. Both the pregnancy and the puerperium were uneventful, and examination revealed no abnormal signs at this time, with no evidence of heart-disease or phlebitis. She had had 2 previous pregnancies (in 1951 and 1954) and in the second thrombosis of the right femoral vein had developed.

The patient was readmitted on June 2, 1958. For three months she had noticed increasing fatigue and dyspnœa, with loss of appetite and weight. For two weeks she had had cough with hæmoptysis and right pleural pain. On examination she was extremely ill and dyspnœic. The pulse-rate was 112 per minute with venous pressure raised 7 cm. and sacral œdema. There was a pulmonary systolic thrill and loud murmur, with normal pulmonary second sound. A pleural rub was heard in the right axilla. A chest radiograph showed a normal heart. The lung fields were clear apart from a small opacity in the right upper zone (fig. 1). An electrocardiogram showed right ventricular strain (fig. 2).

The patient remained very breathless and died suddenly on June 5, 1958. Postmortem examination showed both main pulmonary arteries to be blocked by adherent thrombus several weeks old. There was an infarct in the right lower lobe and thrombosis of the right femoral and calf veins.

Case 2.—A man, aged 72, was admitted in September, 1955, having had dyspnœa for three weeks and right pleural pain and hæmoptysis for four days. He had had large varicose veins for twenty years, but no recent phlebitis. He was afebrile, with

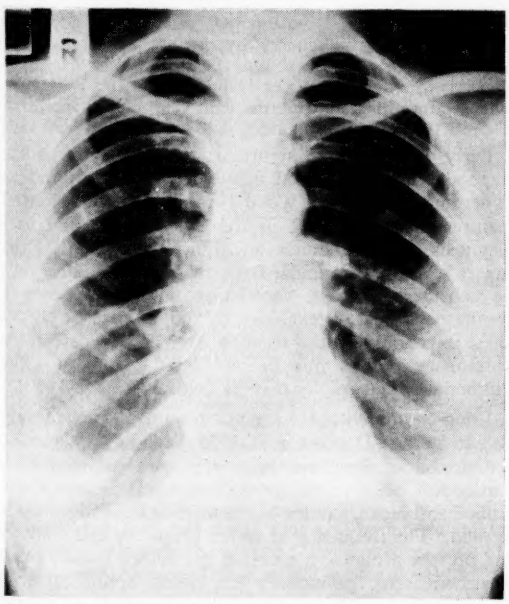

Fig. 1—Case 1: chest X-ray, showing opacity in right upper zone.

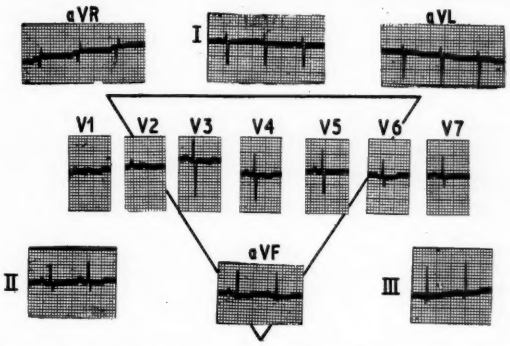

Fig. 2—Case 1: electrocardiograph, with changes indicating right ventricular strain.

râles and a pleural rub at the right lung base. An electrocardiogram showed small R waves with T-wave inversion in lead V_1 but no other abnormality. Pneumonia was diagnosed.

The patient recovered, but from December, 1957, noticed increasing exertional dyspnœa and fatigue. When he was readmitted in September, 1959, there was no orthopnœa, but he could walk only very slowly on flat ground and was breathless on dressing. Examination showed cyanosis, regular cardiac rhythm, and gross congestive heart-failure with systolic venous pulsation to the jaw. The heart was enlarged with a tapping impulse. A loud tricuspid systolic murmur was heard, and in the pulmonary area there was a high-pitched systolic murmur with accentuated pulmonary second sound. A chest radiograph and screening showed right sided cardiac enlargement with prominent main pulmonary arteries which pulsated poorly (fig. 3). An electrocardiogram (fig. 4) confirmed right ventricular hypertrophy.

The heart-failure was controlled. Treatment with anticoagulants continues, so far without much improvement.

In all the remaining 8 patients there was clinical evidence of right ventricular hypertrophy; the pulmonary second sound was accentuated without loud pulmonary murmurs, and in 3 a third heart sound was heard. Auricular

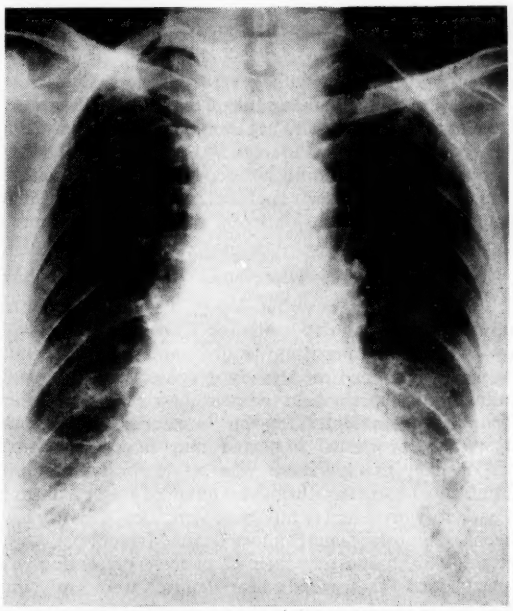

Fig. 3—Case 2: chest X-ray, showing right-sided cardiac enlargement and prominent main pulmonary arteries.

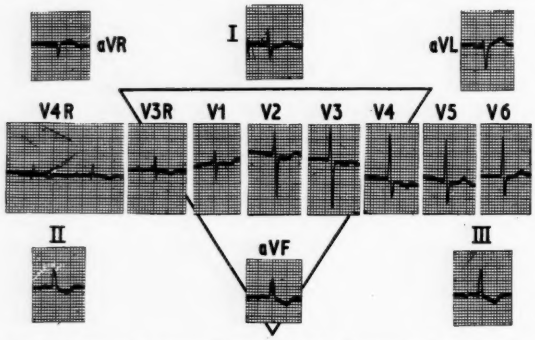

Fig. 4—Case 2: electrocardiograph, with changes indicating right ventricular hypertrophy.

fibrillation was present in 7 of the 8. Chest radiographs and screening showed generalised cardiac enlargement, predominantly affecting the right ventricle. Electrocardiograph evidence of right ventricular hypertrophy was present in 5 of the 8. The emboli had arisen from long-standing varicose veins in 4 cases, and from thrombophlebitis in the remaining 6. Pulmonary embolism was recurrent in 7 patients, with periods of 3 months to 5 years (average 23·3 months) from first to latest recurrence.

In addition to case 1 (see above) 2 patients died. A post-mortem examination was carried out on 1 of these, confirming the diagnosis:

Case 3.—A woman, aged 83, was admitted in November 1958. For many years large varicose veins had been present, and she had been known to be hypertensive for ten years. Over the previous year dyspnœa and angina pectoris had developed. Examination showed auricular fibrillation, with blood-pressure 185/95 mm. Hg, a thrombosed vein in the right calf, and an infarct at the base of the right lung.

The patient improved but was readmitted in January, 1959, with increasing dyspnœa. There was now severe congestive heart-failure, and she died. Postmortem examination showed multiple emboli in the small and medium pulmonary arteries. There was moderate left ventricular hypertrophy, and the coronary arteries were patent though narrowed in places to half the normal lumen.

Of the 10 patients with severe dyspnœa, 3 are now receiving prolonged anticoagulant treatment. Progress is satisfactory in 2, but there has been no improvement in the 3rd (case 2). 3 patients are dead. 1 patient, who had two emboli over a five-month period, has had no recurrence over a further eighteen months. 3 patients had single emboli fifteen months, sixteen months, and eighteen months before review.

Discussion

This study suggests that severe disability may often result from pulmonary embolism. Of the 68 survivors reviewed, 10 had persistent troublesome symptoms and a further 9 remained moderately dyspnœic. In 2 patients pulmonary hypertension with right-ventricular failure was clearly present. In the remainder with severe dyspnœa, myocardial ischæmia may have been partly responsible, though there was no previous disability. Established auricular fibrillation followed the embolism in 8 patients with severe or moderate symptoms and may have been an important contributory factor. In contrast, Owen et al. (1953) found that their 12 patients presenting with unexplained right-sided heart-failure were in sinus rhythm. The absence of many of the classical features of pulmonary hypertension does not exclude pulmonary obstruction; for several workers have reported dyspnœa, fatigue, and cough long before right ventricular hypertrophy was recognisable (Petch 1951, Owen et al. 1953, Ball et al. 1956).

Occlusion of the pulmonary arterioles by multiple or recurrent emboli is an accepted cause of chronic right-sided heart failure but is usually thought to be rare (Ljungdahl 1928, Barnes and Yates 1929, Belt 1939, Covey 1943, Carroll 1950, Petch 1951). Wood (1956) describes only 5 cases. These patients may present with venous thrombosis and acute embolic episodes. Sometimes, unexplained right ventricular hypertrophy and failure develop (Owen et al. 1953, Davison et al. 1956). The diagnosis is often made only at necropsy (Belt 1939).

Obstruction of the main pulmonary arteries by massive thrombus is also diagnosed more often postmortem than in life (Schein et al. 1958). The condition may well be commoner than is suspected, for Zollinger and Hensler (1958) found 68 cases of longstanding massive embolic obstruction in 4000 necropsies. Full clinical details were available in 14 of their patients, in only 3 of whom had the diagnosis been suspected in life. Heart-failure in the remaining 11 patients was usually attributed to myocardial ischæmia. The majority of these massive occlusions are due to pulmonary embolism rather than thrombosis in situ, though no certain decision is possible in the absence of a history of phlebitis or embolus. Thus, Ball et al. (1956) thought that 16 of their 23 cases were embolic.

The clinical picture of pulmonary-artery obstruction is characteristic.

Exertional dyspnœa is predominant, often without orthopnœa. There may be a dry cough. Recurrent pleural pain and hæmoptysis occur, in association with recurrent emboli. Patients complain of tiredness and may faint, especially on exercise (Ball et al. 1956, Davison et al. 1956). Physical signs include cyanosis, a small pulse, and right-ventricular hypertrophy. The venous pressure may be raised, sometimes with tricuspid incompetence. The pulmonary second sound is normal or soft, with a pulmonary systolic murmur due to partial occlusion of the main pulmonary artery (Owen et al. 1953). A peripheral source of emboli is often recognised. Radiologically, there is enlargement of the right side of the heart. The main pulmonary arteries are large but pulsate poorly, and the peripheral lung fields are clear because of oligæmia (Shapiro and Rigler 1948, Hamelin and Eyer 1951). The electrocardiogram confirms right ventricular hypertrophy (Carroll 1950, Owen et al. 1953, Ball et al. 1956, Wood 1956)

Early diagnosis is important, so that anticoagulant treatment may be started before irreversible pulmonary hypertension develops (Wood 1956). Many characteristic features may be absent in the early stages, and early diagnosis depends much on clinical suspicion. Other causes of right ventricular hypertrophy and failure must be considered. Right ventricular failure secondary to respiratory disease is excluded by the absence of chronic chest infections. Mitral stenosis, atrial septal defect, and pulmonary stenosis must be considered (Ball et al. 1956). Pulmonary angiography may be helpful (Carroll 1950).

Long-continued anticoagulant treatment proved valuable in 2 cases (Davison et al. 1956, Wood 1956), and 2 of the present series have improved with anticoagulants. Initial rest helps to reduce pulmonary hypertension. If emboli still recur, ligation of the inferior vena cava may be needed. The frequency of severe persisting symptoms in the present group suggests that protracted anticoagulant treatment after pulmonary embolism would often be justifiable.

Summary

136 cases of pulmonary embolism were diagnosed in an 800-bed general hospital over three years. 71 patients survived the embolism, and 68 of these were reviewed after an average period of 17·6 months.

10 had severe persisting disability, 2 with obvious pulmonary hypertension. 9 others had moderate persisting dyspnœa.

With embolic pulmonary-artery obstruction anticoagulants should be started at once in order to prevent irreversible pulmonary hypetension.

I am grateful to the physicians and surgeons of the Central Middlesex Hospital, especially Dr. Horace Joules and Dr. Keith Ball, for help and for permission to study their patients. I thank Dr. Arthur Willcox for advice in the preparation of this paper.

REFERENCES

Ball, K. P., Goodwin, J. F., Harrison, C. V. (1956) *Circulation*, **14**, 776.
Barnes, A. R. (1937) *J. Amer. med. Ass.* **109**, 1347.
— Yates, W. M. (1929) *Med. Clin. N. Amer.* **12**, 1603.
Belt, T. H. (1939) *Lancet*, ii, 730.
Carroll, D. (1950) *Amer. J. Med.* **9**, 175.
Covey, G. W. (1943) *Ann. intern. Med.* **18**, 851.
Davison, P. H. Armitage, G. H., McIlveen, D. J. S. (1956) *Lancet*, ii, 224.
Elliott, B. A., Gresham, G. A., Phear, D. N. (1960) *Brit. med. J.* i, 1320.
Hamelin, J., Eyler, W. R. (1951) *Radiology*, **56**, 689.
Ljungdahl. M. (1928) *Dtsch. Arch. klin. Med.* **160**, 1.
Magidson, O., Jacobson, G. (1955) *Brit. Heart J.* **17**, 207.
Owen, W. R., Thomas, W. A., Castleman, B., Bland, E. F. (1953) *New Engl. J. Med.* **249**, 919.
Petch, C. P. (1951) *Lancet*, i, 1346.
Schein, C. J., Rifkin, H., Hurwitt, E. S., Lebendiger, A. (1958) *Arch. intern. Med.* **101**, 592.
Shapiro, R., Rigler, L. G. (1948) *Amer. J. Roentgenol.* **60**, 460.
Wood, P. (1956) Diseases of the Heart and Circulation. London.
Zollinger, H. U., Hensler, L. (1958) *Schweiz. med. Wschr.* **88**, 1227.

ENZYME DEFICIENCY IN HÆMOLYTIC DISEASE OF THE NEWBORN

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THE susceptibility of red blood-cells to hæmolysis has been shown to be associated with certain inherited errors of metabolism within the cells. Thus the hæmolysis in Negroes following primaquine therapy is associated with a lowered level of reduced glutathione in the red blood-cells, and when these cells are incubated in vitro with acetyl phenylhydrazine the level of reduced glutathione falls notably (Beutler et al. 1955, 1957). These changes have been related to a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G.-6-P.D.) in these cells (Carson et al. 1956). This enzyme has also been shown to be deficient in patients in whom hæmolytic episodes have followed ingestion of sulphonamides, *p*-aminosalicylic acid, naphthalene, and *Vicia faba* (Sansone and Segni 1958, Szeinberg et al. 1958). This deficiency appears to be inherited as a sex-linked gene of intermediate dominance (Browne 1957).

In several recent reports of cases in which hæmolytic episodes have been associated with G.-6-P.D. deficiency there was a history of neonatal jaundice.

Such a history was obtained in the case of a 4-year-old Italian child who had a severe hæmolytic episode following sulphafurazole therapy (Newton and Bass 1958). There were similar histories in cases of children with relapsing hæmolytic anæmia associated with G-6-P.D. deficiency (Shahidi and Diamond 1959, Zinkham and Lenhard 1959). In the case of a 32-year-old Jewess in whom a severe hæmolytic episode following sulpahmethoxpyridazine therapy was associated with G.-6-P.D. deficiency, the patient gave a history of having lost 3 children with severe neonatal jaundice (Vella and Phoon 1959). Smith and Vella (1960) have examined blood specimens from 20 cases of hæmolytic disease in the neonatal period (19 Chinese and 1 Malay) unassociated with ABO or Rh incompatibility, and found G.-6-P.D. deficiency in every case but 1.

The following report deals with three Malay families in which there seems to be a strong association between neonatal hæmolytic disease and G.-6-P.D. deficiency.

Methods

Glucose-6-phosphate dehydrogenase deficiency was detected by the rapid colorimetric method of Motulsky and Campbell (cited by Vella 1959). The enzyme catalyses the reaction in which reduced triphosphopyridine nucleotide (T.P.N.H.) is generated:

$$\text{Glucose-6-phosphate} + \text{T.P.N.} = \text{6-phosphogluconic acid} + \text{T.P.N.H.} + H^+$$

The dye brilliant cresyl-blue, which is colourless in the reduced state, is used as an indicator of this reaction and the time taken for decolorisation under standard conditions is recorded in the test. Enzyme deficiency has been confirmed by spectrophotometric method in blood samples which fail to decolorise in 120 minutes. In all samples reported below as deficient, decolorisation had not occurred in 3 hours.

All blood samples were examined for abnormal hæmoglobins by paper electrophoresis at pH 8·6 (veronal buffer) and pH 6·5 (citrate buffer).

Alkali-resistant hæmoglobin was estimated by the method of Chernoff (1955).

Case-records

FAMILY 1

The first member of this Malay family to be examined was a 4-day-old male infant.

He was born on Dec. 9, 1959, in the British Military Hospital, Singapore, at full term; delivery was normal and his birth-weight was 7 lb. 2 oz. The mother had been given no drugs during pregnancy or labour, and there was no history of her having sucked moth-balls (Zinkham and Childs 1958). The infant received no vitamin K or other drugs in the period immediately after birth. He was breast-fed and thrived until the fourth day of life.

On the fourth day he was noted to be jaundiced, and the jaundice rapidly deepened until the sixth day when kernicterus developed. At this time there was moderate hepatosplenomegaly but no evidence of any focus of infection. The jaundice slowly cleared over the next seven days, but the neurological signs have persisted. Investigations at that time were as follows: hæmoglobin 11·6 g. per 100 ml., which fell to 6·0 g. per 100 ml. on the eighth day; white blood-cells 12,700 per c.mm. (polymorphs 54%, lymphocytes 42%, monocytes 3%, eosinophils 1%); reticulocytes 3%; serum-bilirubin 18 mg. per 100 ml. (indirect acting). Examination of a peripheral-blood smear revealed anisocytosis, poikilocytosis, normoblastosis, and no Heinz bodies. The erythrocyte osmotic fragility was normal. The direct and indirect Coombs tests were negative. The infant's blood was type A, CDe/CDe (R_1 R_1) and its mother type A, CDe/CDe (R_1 R_1). No incompatibility was demonstrated between the infant's cells and maternal serum at 4°C, room-temperature, or 37°C in either saline or albumin. Liver-function tests showed: thymol turbidity 3 units, zinc-sulphate flocculation 4 units, and alkaline phosphatase 19·2 King-Armstrong units. The Wassermann reaction and Kahn test were negative. The fæces contained stercobilin, and urine analysis revealed increased amounts of urobilinogen. There were no abnormalities of hæmoglobin on paper electrophoresis at pH 8·6 or pH 6·5, only hæmoglobins A and F being present. G.-6-P.D. activity was estimated by the method outlined above, and the infant's cells were shown to be enzyme-deficient.

For this reason family studies were done. The parents were healthy and there were five siblings, two female and three male. There was no history of consanguinity. One

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male sibling had died of an obscure illness in his village, aged 9 months. There were no abnormalities on physical examination of any of the family, and investigations of their blood showed normal levels of hæmoglobin and serum-bilirubin. In no case was the reticulocyte-count greater than 1% of the total red-cell count. There were no abnormalities of hæmoglobin at pH 8·6 or pH 6·5, and in all cases the level of alkali-resistant hæmoglobin was less than 2%. G.-6-P.D. deficiency was demonstrated in both parents and in one female and two male siblings. (One male and one female sibling were not available for examination.)

FAMILY 2

This family consisted of the parents and two male children, both of whom were deeply jaundiced from the 3rd day of life until the end of the 2nd week. In addition there had been four other pregnancies, the infants all having died, deeply jaundiced, between the fifth and the eighth day of life. These infants had all been born at full term of normal deliveries and there was no history of the mother or infants receiving any drugs. All the infants were males. Two of them were seen in the British Military Hospital.

The first of these two was a male child weighing 7 lb. 2 oz. who was born on Oct. 28, 1958, of a normal delivery. He thrived until the third day of life when he was noted to be jaundiced; there was no hepatosplenomegaly and no evidence of infection. The jaundice rapidly deepened and the child died of kernicterus on the seventh day of life. Investigations on admission (4th day of life) showed: hæmoglobin 7·2 g. per 100 ml.; white blood-cells 14,300 per c.mm. (polymorphs 64%, lymphocytes 30%, monocytes 3%, eosinophils 3%). A peripheral-blood smear revealed anisocytosis, poikilocytosis, and normoblastosis. Serum-bilirubin 10 mg. per 100 ml. (all indirect acting). Direct and indirect Coombs tests negative. The infant's blood-group was type B, CDe/CDe (R_1 R_1), and the mother's type B, CDe/CDe (R_1 R_1). No incompatibility was demonstrated between the infant's cells and maternal serum at 4°C, room-temperature, or 37°C in either saline or albumin. The urine contained increased amounts of urobilinogen. Liver-function tests: thymol turbidity 1 unit, zinc-sulphate flocculation 1 unit, alkaline-phosphatase 10 King-Armstrong units. The Wassermann reaction and Kahn test were negative.

The second child was a male weighing 5 lb. at birth. This child became deeply jaundiced on the 2nd day of life and died of kernicterus on the 5th day. Investigations on the 4th day of life showed: hæmoglobin 9·6 g. per 100 ml. A peripheral-blood smear revealed much anisocytosis, poikilocytosis, and normoblastosis. Serum-bilirubin 17 mg. per 100 ml. (all indirect acting). Direct and indirect Coombs tests were negative. This infant's blood was type B, CDe/CDe/ (R_1 R_1), and no incompatibility was shown between the infant's cells and maternal serum at 4°C, room-temperature, and 37°C in either saline or albumin. The Wassermann reaction and Kahn test were negative.

In view of these unexplained deaths the parents and two living children were examined. There was no abnormality on physical examination, and investigations revealed normal level of hæmoglobin and serum-bilirubin. Saline fragility tests were normal. There were no abnormalities of hæmoglobin at pH 8·6 and pH 6·5, and in no case was the level of alkaline-resistant hæmoglobin more than 2% of the total hæmoglobin. G.-6-P.D. studies showed deficient enzyme activity in the father and two siblings and normal activity in the mother.

FAMILY 3

The patient was a 4-year-old boy.

He was born in a kampong (Malay village) of a full-term normal delivery, weighing at birth 5 lb. 6 oz. No drugs had been given to the mother or child. He was well until the 3rd day of life when he was noted to be jaundiced. The jaundice deepened until the 6th day when he had several convulsions, and after this he lay in a position of opisthotonos for several days. His jaundice cleared slowly over the next two weeks. The child was slow to sit up and had never walked or talked. There had been no further episodes of jaundice.

On examination the child was mentally and physically retarded. The mucous membranes were pale; no hepatosplenomegaly. The limbs were severely hypertonic, and pronounced athetosis was noted. The history and findings pointed to the diagnosis of kernicterus with severe neurological sequelæ.

Investigations showed: hæmoglobin 9·0 g. per 100 ml.; red blood-cells 3,350,000 per c.mm.; white blood-cells 10,100 per c.mm. (polymorphs 83%, lymphocytes 14%, monocytes 1%, eosinophils 2%). A peripheral-blood smear revealed microcytosis, anisopoikilocytosis, and occasional normoblasts. Reticulocytes 3%. Saline fragility test normal. Direct and indirect Coombs test negative. The child's blood was type O, cDE/cDE (R_2 R_2), and the mother's type O, cDE/cDE (R_2 R_2). No incompatibility was demonstrated between the child's cells and maternal serum at 4°C, room-temperature, and 37°C in saline or albumin. Liver-function tests: serum-bilirubin 1 mg. per 100 ml., zinc-sulphate flocculation 2 units, thymol turbidity 3 units. The urine contained a slightly increased amount of urobilinogen. There was no abnormality of hæmoglobin at pH 8·6 or pH 6·5. Alkaline-resistant hæmoglobin was less than 2%. Enzyme studies showed deficient G.-6-P.D. activity in the red blood-cells. The hæmotological findings suggested that this child had a low-grade hæmolytic process, though no acute episode had occurred since the neonatal period.

Examination of the parents and one female sibling revealed no clinical or hæmatological abnormality. There were no abnormalities of hæmoglobin on electrophoresis and G.-6-P.D. studies showed normal enzyme activity. One of the parents must have been a carrier for this deficiency. Alving et al. (1958) have pointed to the occasional discrepancy between in-vitro tests of enzyme deficiency and and in-vivo susceptibility to hæmolysis.

FURTHER FAMILIES STUDIED

So far nine further Malay families have been studied. In each of these families one or more infants were jaundiced from about the 3rd day until the 2nd week of life. Unlike families 1–3 there was no evidence of a hæmolytic basis for this jaundice, and in no case was G.-6-P.D. deficiency demonstrated in either the infant or any member of the family.

Discussion

In the three Malay families described here G.-6-P.D. deficiency was associated with severe hæmolytic disease in the newborn, resulting in kernicterus. In each case ABO and Rh incompatibility, infection, and hæmoglobinopathy were excluded; and, so far as possible, drug sensitisation were also excluded. This seems unlikely to be a chance association. G.-6-P.D. deficiency is not common in Malaya; Vella (1959) found no cases in blood specimens from 90 Malay blood-donors. Hæmolytic disease is also uncommon, the cases described here being the only instances in 600 Malay births in the British Military Hospital, Singapore, between 1957 and 1959. (It is exceedingly rare to find a Rh-negative Malay.)

The mechanism of the hæmolysis in these cases is uncertain. Possibly a so-far unrecognised external sensitising agent is responsible, though this seems unlikely. It seems more likely that, under certain circumstances, hæmolysis can occur without any such agent in patients with susceptible red blood-cells. A history of neonatal jaundice is common in G.-6-P.D.-deficient families, and

possibly the normal stresses of the perinatal period are sufficient to cause hæmolysis in infants with susceptible cells. Further work is needed on this.

Summary

A history of neonatal jaundice is not uncommon in patients with a deficiency of glucose-6-phosphate dehydrogenase in their red blood-cells.

In three Malay families severe hæmolytic jaundice in the neonatal period was associated with deficiency of this enzyme. The mechanism is unknown.

I wish to thank Dr. F. Vella, late of the department of biochemistry, University of Malaya, for performing the glucose-6-phosphate dehydrogenase studies on these patients; Captain R. D. Williams, R.A.M.C., for collecting blood specimens from several of the Malay families; Lieut.-Colonel J. P. Baird, R.A.M.C., and Major S. E. M. Jarvis, R.A.M.C., for their advice and interest in this work; and the command pathology laboratory, FARELF, for their cooperation.

REFERENCES

Alving, A. S., Kellermeyer, R. W., Tarlov, A., Schrier, S., Carson, P. E. (1953) *Ann. intern. Med.* **49**, 240.
Beutler, E., Dern, R. J., Flanagan, C. L., Alving, A. S. (1955) *J. Lab. clin. Med.* **45**, 286.
— Robson, M. J., Buttenwieser, E. (1957) *ibid.* **49**, 84.
Browne, E. G. (1957) *Bull. Johns Hopk. Hosp.* **101**, 115.
Carson, P. E., Flanagan, C. L., Ickes, C. E., Alving, A. S. (1956) *Science*, **124**, 484.
Chernoff, A. I. (1955) *New Engl. J. Med.* **253**, 322.
Newton, W. A., Jr., Bass, J. C. (1958) *A.M.A. J. Dis. Child.* **96**, 501.
Sansone, G., Segni, G. (1958) *Boll. Soc. ital. Biol. Sper.* **34**, 327.
Shahidi, N. T., Diamond, L. K. (1959) *Pediatrics*, **24**, 245.
Smith, G. D., Vella, F. (1960) *Lancet*, i, 1133.
Szeinberg, A., Sheba, C., Adam, A. (1958) *Nature, Lond.* **181**, 1256.
Vella, F. (1959) *Med. J. Malaya*, **13**, 298.
— Phoon, W. O. (1959) *ibid.* p. 309.
Zinkham, W. H., Childs, B. (1958) *Pediatrics*, **22**, 461.
Lenhard, R. E., Jr. (1959) *J. Pediat.* **55**, 319.

PROPHYLACTIC ISONIAZID IN NURSES IN A TUBERCULOSIS HOSPITAL

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TUBERCULOSIS as an occupational hazard in nurses has declined sharply in the United Kingdom (*Lancet* 1959). The King George V Hospital for tuberculosis has 1300 beds for non-European patients. Over 90% of adults have a positive sputum on admission. Two-thirds of patients have far-advanced pulmonary tuberculosis. The death-rate has declined in recent years, but 12·5% of patients die in hospital, half of these within a month after admission. Here the hazard remains.

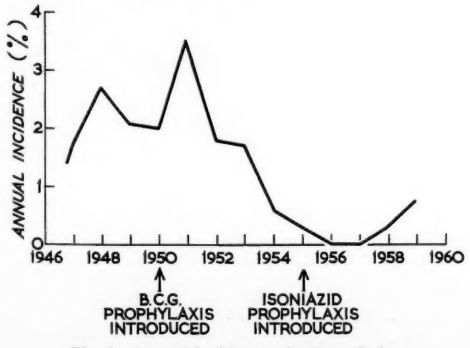


Fig. 1—Annual incidence of tuberculosis.

TABLE I—PREVALENCE OF TUBERCULOSIS ON APPOINTMENT (MAY 20, 1946, TO DEC. 31, 1958)

Race	Total X-rayed	No. with tuberculosis
Bantu:		
Zulu	894	25 (2·8%)
Xhosa	479	10 (2·1%)
Other	151	3 (2·0%)
Total	1524	38 (2·5%)
Indian	211	3 (1·4%)
Coloured	112	1 (0·9%)
All races	1847	42 (2·3%)

X-ray results not known for 37 nurses (2·0%).

Wards in this hospital consist of 60-bed units. The nursing team comprises about 15 nurse-aides led by fully-trained nurses. Figures in this paper refer to the non-European nurse-aides only, of whom there were about 1900.

The first non-European nurse-aides were appointed to the staff on May 20, 1946. Young Bantu, Coloured, and Indian women who can read and write and have passed standard VI or VII are given a three-month elementary nursing course with a bias towards practice rather than theory (Dormer 1950). The nurse-aides then enter the wards, but continue to attend lectures for about eighteen months. Kindness to the sick, and the performance of simple actions which make sick people comfortable, are the basis of training.

The usual methods of control of tuberculous infection and early detection of cases among the staff are applied, including two-monthly to three-monthly X-rays, tuberculin-testing, and regular re-testing of negative reactors. In addition, B.C.G. prophylaxis was introduced in 1950, and isoniazid prophylaxis in 1955.

Findings

Annual Incidence of Tuberculosis

The annual incidence, which is taken as the number of cases expressed as a percentage of the mid-year establishment, is shown in fig. 1. Between May 20, 1946, and December, 1959, 55 cases of tuberculosis arose amongst non-European nurse-aides.

Prevalence of Tuberculosis on Appointment

The prevalence of tuberculosis on appointment is, in some degree, an indication of the amount of tuberculosis likely to develop later, as environmental factors may modify the attack-rate although exposure is constant. Thus, the Prophit survey (Daniels et al. 1948) found a higher prevalence of tuberculosis on entry among Irish and Welsh nurses (2·8%) than among others (1·1%), and also a higher morbidity-rate amongst Irish and Welsh

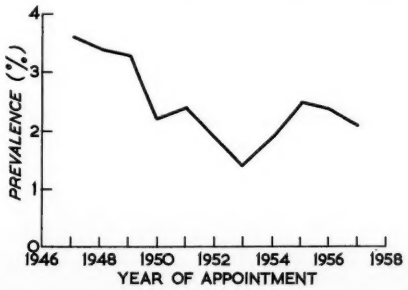


Fig. 2—Prevalence of tuberculosis on appointment (Bantu nurses only): three-year moving averages.

nurses (27·1 per 1000 years) than amongst others (10·7 per 1000 years).

The prevalence of tuberculosis on appointment of nurses in this series was 2·3% (table I). The prevalence has not changed much since 1950, but the higher figures of the early years have not been reached again (fig. 2). It is improbable that changes in prevalence account for the lower incidence since 1955.

Length of Service

The incidence of tuberculosis has been greatest in the second, third, and fourth years of service (fig. 3). The structure of the staff as regards length of service does not account for the fall in incidence in recent years (fig. 4).

Tuberculin Sensitivity on Appointment

The percentage of nurses tuberculin-positive on appointment was 83·9 (table II). A year-by-year analysis

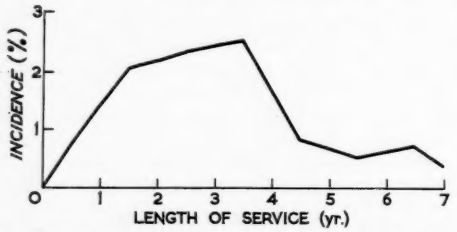
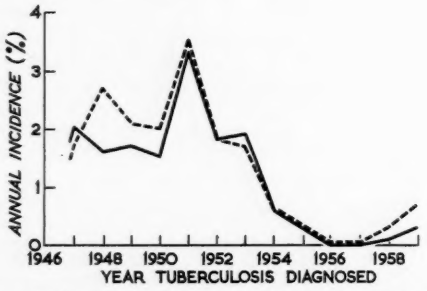


Fig. 3—Incidence of tuberculosis related to length of service.

of these figures does not show a rising or falling trend (fig. 5). The incidence of tuberculosis does not differ significantly according to whether the nurses were tuberculin positive or negative on appointment (table III). Over 80% of nurses who were tuberculin-negative on appointment and who did not receive B.C.G. became tuberculin-positive within a year after appointment. Nevertheless, of the 12 nurses who were initially tuberculin-negative and in whom tuberculosis developed, the lesions developed in only 3 at the time of conversion or soon after (table IV). The remaining 9 cases in initially tuberculin-negative nurses developed thirteen months to five years after conversion. The majority of initially tuberculin-negative nurses thus became tuberculin-positive without developing detectable tuberculous lesions and may be regarded as augmenting the number of tuberculin-positive persons liable to develop tuberculosis. In any event, the total number tuberculin-negative on appointment was small, and the major problem is control of tuberculosis among nurses who are already tuberculin-positive on appointment.



——— Incidence (%) standardised for length of service against 1952.

- - - - - Incidence (%): crude figures as in fig. 1.

Fig. 4—Annual incidence of tuberculosis related to length of service.

TABLE II—TUBERCULIN SENSITIVITY ON APPOINTMENT (MAY 20, 1946, TO DEC. 31, 1958)

Race	Total known	No. tuberculin-positive
Bantu:		
Zulu	876	730 (*83·3%*)
Xhosa	466	443 (*95·1%*)
Other Bantu	138	121 (*87·7%*)
Total	1480	1294 (*87·4%*)
Indian	205	129 (*62·9%*)
Coloured	110	83 (*75·5%*)
All races	1795	1506 (*83·9%*)

Tuberculin sensitivity not known for 89 nurses (4·7%).

B.C.G. Prophylaxis

B.C.G., at best, could help only those originally tuberculin-negative—i.e., 16% of the staff. B.C.G. was first given in 1950 to those members of the staff who had remained tuberculin-negative, and gradually those found negative on appointment were included in the scheme. This procedure was followed until towards the end of 1955 when B.C.G. vaccination was discontinued. It was recommenced in the middle of 1959. In all, 83 nurses who were originally tuberculin-negative received B.C.G. before the end of 1955, and tuberculosis developed in 3 of these (3·6%) (cases 1–3).

Isoniazid Prophylaxis

In September, 1955, isoniazid prophylaxis was introduced. All nurses received isoniazid 300 mg. daily in a single dose. No case of tuberculosis was detected thereafter until April, 1958, when 1 case was detected; and 3 further cases occurred in 1959 (cases 3–6). Thus,

TABLE III—INCIDENCE OF TUBERCULOSIS RELATED TO INITIAL TUBERCULIN REACTION

Tuberculin reaction of appointment	No. of nurses	No. of cases of tuberculosis	Incidence (%)
Positive	1506	42	2·8
Negative ..	289	12	4·2

of some six hundred nurses who have received isoniazid prophylactically, 4 have developed tuberculosis. With isoniazid prophylaxis, the incidence of tuberculosis has fallen irrespective of tuberculin sensitivity on appointment (table V). Thus far, no case of tuberculosis has occurred in a nurse who was tuberculin-negative at the start of isoniazid prophylaxis (table VI). Given prophylactically, isoniazid has benefited both tuberculin-negative and tuberculin-positive nurses.

The incidence was low in 1954 and 1955, before the

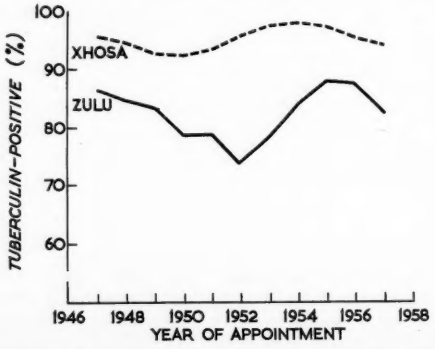


Fig. 5—Tuberculin reaction on appointment: three-year moving averages.

TABLE IV—DATA ON 12 CASES OF TUBERCULOSIS IN NURSES WHO WERE TUBERCULIN-NEGATIVE ON APPOINTMENT

Time of conversion after appointment (mos.)	Time between conversion and manifestation of tuberculosis	Type of tuberculosis	Time of conversion after B.C.G. administration
Under 3 ..	1. 13 mos.	Generalised	..
	2. 16 mos.	Minimal	..
	3. 22 mos.	Minimal	..
	4. 3½ yr.	Minimal	..
	5. Over 5 yr.	Moderate	2 mos. (case 3)
3–6	6. Simultaneous	Primary	..
	7. 2 yr.	Minimal	..
6–9	8. Simultaneous	Minimal	..
	9. 17 mos.	Pleural effusion	..
9–12	10. 18 mos.	Minimal	..
12–15 ..	11. 2–3 mos.	Pleural effusion	1 yr. (case 2)
	12. 17 mos.	Minimal	6 weeks (case 1)

introduction of isoniazid prophylaxis. Although these figures are unexpected, the number of cases involved in each year is small, and the low 1954 and 1955 figures may represent chance fluctuations. After the introduction of isoniazid prophylaxis, no case occurred for two and a half years. The crop of cases in 1959 is disappointing.

It is noteworthy that of the 4 cases of tuberculosis that arose after the introduction of isoniazid prophylaxis, 3 were detected while the nurse was on leave or within a month of her return from leave. It is fairly certain that

TABLE V—INCIDENCE OF TUBERCULOSIS RELATED TO TUBERCULIN SENSITIVITY ON APPOINTMENT AND ISONIAZID PROPHYLAXIS

Prophylactic isoniazid	Tuberculin-positive on appointment		Tuberculin-negative on appointment	
	Total	No. of cases of tuberculosis	Total	No. of cases of tuberculosis
Nil	1365	39 (2·9%)	214	11 (5·1%)
Prophylaxis during part or all of service	569	3 (0·5%)	93	1 (1·1%)

nurses did not continue taking isoniazid while on leave, and not impossible that an infection kept at bay by isoniazid flared up on withdrawal of the drug. Of the 51 cases that occurred before the introduction of isoniazid, 7 (13·7%) were detected while the nurse was on leave or within a month after her return from leave. This is the expected proportion in twenty days' leave plus thirty days—i.e., 50/365=13·7%. Accordingly, nurses are now urged to continue taking isoniazid while on leave, and also for three months after leaving the staff.

TABLE VI—INCIDENCE OF TUBERCULOSIS RELATED TO TUBERCULIN SENSITIVITY ON APPOINTMENT AND AT START OF ISONIAZID PROPHYLAXIS ON SEPT. 20, 1955

Date of appointment	Tuberculin reaction on appointment	Subsequent tuberculin reaction	Tuberculin-positive		Tuberculin-negative	
			Total	No. of cases of tuberculosis	Total	No. of cases of tuberculosis
Before Sept. 20, 1955	Positive Negative	Negative on Sept. 20, 1955	287	2 (0·7%)	7	..
		Positive after B.C.G.	28	1		
		Positive without B.C.G.	16	..		
After Sept. 20, 1955			282	1 (0·4%)	42	..
Total			613	4 (0·7%)	49	..

Case-records

Case 1.—A nurse, aged 18 on appointment in June, 1949, was repeatedly tuberculin-negative between then and January, 1950. On April 14, 1950, B.C.G. was given; and on June 2, 1950, she was shown to be tuberculin-positive. On Nov. 24, 1951, X-ray showed slight tuberculous density in the first right interspace; the sputum contained *Mycobacterium tuberculosis*. The condition responded well to treatment with streptomycin and *p*-aminosalicylic acid (P.A.S.). On Sept. 21, 1954, the patient was well, and the lesion quiescent.

Case 2.—A nurse, aged 17 on appointment in March, 1950, was twice that month shown to be tuberculin-negative. B.C.G. was given on April 14, 1950. On May 22, 1951, she was found to be tuberculin-positive. On Aug. 2, 1951, X-ray examination showed a pleural effusion. All investigations for *Myco. tuberculosis* were negative. The disorder responded well to treatment with streptomycin and P.A.S. In November, 1959, the patient was still on the staff, fit, with X-ray clear.

Case 3.—A nurse, aged 21, was tuberculin-negative on appointment in September, 1952. Next month B.C.G. was given, and two months later she was tuberculin-positive. On Sept. 20, 1955, isoniazid prophylaxis was started; and the drug was taken regularly except for periods of leave, the last of which was from March 8 to 30, 1958. On April 9, 1958, X-ray showed early infiltration and cavitation of left apex. Direct and cultural examination of sputum was positive for *Myco. tuberculosis*. The organisms were insensitive to isoniazid at concentrations of 5 to 200 μg. per ml. of medium. On guineapig inoculation the organism caused enlargement of mesenteric nodes and a few foci in the liver—virulence grading 5/18. The patient was treated with 'Dipasic' (isoniazid and P.A.S.) 60 mg. per kg., streptomycin 1 g. daily for thirty days then bi-weekly, and prednisone. In four months the X-ray showed much improvement, and in six months the sputum was negative. On Nov. 1, 1958, the patient resumed duty. A year later she was on duty, fit; X-ray showed residual densities.

Case 4.—A nurse, aged 18, was tuberculin-positive but had a clear chest X-ray on appointment in December, 1951. On Sept. 20, 1955, isoniazid prophylaxis was started, and the drug was taken regularly for some months. Thereafter isoniazid was taken irregularly, and none was taken while the patient was on leave from Jan. 5 to 25, 1959. On Feb. 18, 1959, X-ray showed early infiltration and cavitation in the right upper zone. Cultural examination of sputum for *Myco. tuberculosis* was positive. The organisms were insensitive to isoniazid in a concentration of 5 μg. per ml. of medium, but sensitive to a concentration of 50 μg. per ml. On guineapig inoculation the organism caused lesions of spleen, liver, and lungs—virulence grading 18/18. The nurse was treated with 'Streptoneotizide' (an association of streptomycin and sodium methanesulphonate of isoniazid) 1 g. daily for sixty days, then 1 g. on alternate days, and P.A.S. 12 g. daily. Sputum became negative in a month. X-ray examination showed progressive improvement; and on Oct. 20, 1959, the patient was discharged from hospital.

Case 5.—A nurse, aged 21, was tuberculin-positive but had a clear chest X-ray on appointment on March 1, 1957, when isoniazid prophylaxis was instituted. The patient was on leave from April 4 to 27, 1958. On May 18, 1959, X-ray showed considerable hilar node enlargement. The diagnosis was not proved bacteriologically, but a presumptive diagnosis of tuberculosis was made in the absence of other positive findings. The nurse has remained on duty while receiving treatment.

Case 6.—A nurse, aged 33, was tuberculin-positive but had a clear chest X-ray on appointment in December, 1949. On Sept. 20, 1955, isoniazid prophylaxis was started; but there is some doubt as to whether the drug was taken regularly. On June 8, 1959, the patient went on leave; and on June 24, while still on leave, she was found to have a pleural effusion. The fluid contained *Myco. tuberculosis*. The organism was

fully sensitive to isoniazid in vitro. A guineapig inoculated with the pleural fluid showed tuberculous abscesses of inguinal and iliac nodes and one nodule in the spleen, but no lesion in liver or lungs: virulence grading 8/18. The nurse was treated with streptomycin and isoniazid. She resumed duty on Sept. 14, 1959.

Regularity of Isoniazid Prophylaxis

Nurses take isoniazid under supervision of the ward sisters. They have not all taken it while on leave; and cases 4 and 6 suggested that they did not all take it when at work. On Oct. 2, 1959, this was investigated. All nurse-aides on duty that day were assembled in four groups and were asked to complete a simple questionary about the regularity with which they were taking isoniazid. The questionary was completed by 300 nurses—72·6% of the staff. Nurses did not complete a form if they were off duty. No identification was required on the forms. It is felt that replies were honest and that an analysis gave a reliable picture of the problem.

Isoniazid was taken regularly by 203 nurses (68%) of those who answered the questionary). The proportion of nurses taking isoniazid regularly rose from 56% of 131 nurses with four or more years of service to 87% of 60 nurses with less than a year's service. The longer a nurse is on the staff, the greater is her opportunity for failing to take isoniazid; but this cumulative effect is not the sole factor. That a nurse took isoniazid irregularly, but nevertheless took it on the day of the questionary or the day before, suggests that she was still attempting to take it. If one accepts this inference, then of 58 nurses with four or more years' service who took isoniazid irregularly, 29 were still attempting to take it; whereas of 26 with less than three years' service, 19 were still attempting to take it. A higher proportion of the nurses with long service had apparently given up the attempt.

The old problem of self-administration of drugs has presented itself in another guise. Constant reminders are necessary, particularly as the years of high incidence on the staff become more remote. Since the time of the questionary, supervision and propaganda have been intensified.

The commonest reason for not taking isoniazid, named by 37 nurses, was itch either alone or combined with other symptoms; 31 gave no reason; 10 admitted forgetfulness; 7 complained they became too fat. Nurses were asked to report their individual difficulties and discuss them with a doctor. Few came forward, presumably because their anonymity would be forfeit.

Discussion

Tubercle bacilli recovered from 3 nurses (cases 3, 4, and 6) who developed tuberculosis after a period of isoniazid prophylaxis showed various degrees of isoniazid resistance in vitro and of virulence for guineapigs. All these nurses have responded satisfactorily to treatment with isoniazid or its derivatives and streptomycin with or without P.A.S. The outcome, judged by speed with which sputum was converted, the X-ray cleared, and the nurse returned to duty, compares favourably with the outcome of cases in which tuberculosis developed without previous isoniazid prophylaxis.

Isoniazid prophylaxis is completely effective in babies (Dormer et al. 1959) and calves (Dormer et al. 1960). It is less certain in adults who can choose not to take it. Nevertheless, it is worth while in a group of people where exposure to tuberculous infection is high.

Summary

In September, 1955, prophylaxis with isoniazid 300 mg. daily was initiated in a tuberculosis hospital among non-European nurse-aides. These numbered about 600, of whom 16% were tuberculin-negative on appointment.

In the next two years no case of tuberculosis was diagnosed in this group; in the third year only 1 case was diagnosed; but in the fourth year 3 cases were diagnosed.

After four years, 32% of nurses were found to be taking isoniazid irregularly, and 68% regularly.

REFERENCES

Daniels, M., Ridehalgh, F., Springett, V. H. (1948) Tuberculosis in Young Adults. London.

Dormer, B. A. *S. Afr. med. J.* (1950) **24**, 552.

— Harrison, I., Swart, J. A., Vidor, S. R. (1959) *Lancet*, ii, 902.

— Hobbs, W. B., Martinaglia, G. (1960) Unpublished.

Lancet (1959) ii, 121.

PERITONEAL DIALYSIS IN SALICYLATE INTOXICATION

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WE report three cases of severe salicylate intoxication successfully treated by peritoneal dialysis. Though this method has shown considerable experimental promise in dogs, it has not, as far as we know, been used before in man.

Case-reports

Case 1.—A $2^1/_2$-year-old boy was admitted with a history of a mild attack of measles, which began four days before admission, and was complicated by progressive dyspnœa and drowsiness during the last twelve hours. At the onset of dyspnœa the child was given penicillin, but the condition rapidly became worse. When questioned the mother denied that she had given the child aspirin.

He was gravely ill and had a fading morbilliform rash, a dry skin, and peripheral vascular collapse. There were no clinical signs or radiographic evidence of pneumonia, but there was inspiratory effort and the respiratory rate was 32 per minute. Temperature was 100°F and the pulse-rate 120 per minute. A serum-ionogram showed sodium of 141 mEq. per litre, potassium 3 mEq. per litre, bicarbonate 10·8 mEq. per litre, and chloride 110 mEq. per litre. The low serum-bicarbonate suggested the need for further investigation, and the serum-salicylate was found to be 38·2 mg. per 100 ml. The leucocyte-count was 26,100 per c.mm (suggestive of dehydration), and the blood-glucose was 85 mg. per 100 ml. No urine could be obtained by catheterisation.

From previous clinical experience with these cases we realised that despite careful control of serum-electrolyte changes some patients still died. There did not seem to be sufficient time to set up the artificial kidney, and peritoneal dialysis was therefore carried out at once.

Two polyethylene tubes were inserted into the peritoneal cavity, one on each side, between the umbilicus and the superior iliac spine. During the next four hours 4 litres of Hartman's solution * were dripped through the left catheter and collected from the right. There was some seepage alongside the tubing, so that not all the fluid removed from the peritoneal cavity was collected.

The breathing eased after the first hour and the child looked much better after the second. There was rapid improvement following 5% dextrose given intravenously and recovery was then uninterrupted. The dialysate contained 7·3 mg. per 100 ml. of salicylate. Owing to the seepage the total amount removed

* Hartman's solution: sodium 130 mEq., potassium 40 mEq., calcium 2·7 mEq., chlorine 109 mEq., lactate 28 mEq.

could not be calculated exactly. If all the fluid ran through, only 929 mg. of salicylate were removed.

On further questioning the mother said she had given the child one 5-grain aspirin tablet every four hours for the last three days of his illness. She believed that salicylates were quite harmless, and because of the initial time lapse, had not thought that this medication could be connected with her son's illness.

Case 2.—A 5-month old girl was admitted in coma with rapid rhythmic dyspnœa, and chickenpox. The respiratory rate was 45 per minute, the temperature 103°F, pulse-rate 160 per minute.

The child had dry skin and such severe dehydration that no blood could be obtained from the collapsed peripheral veins. Coarse limb-twitching was noted, and a few scattered râles were heard in the chest. An X-ray of the chest was said to show "early inflammatory infiltration in the right upper and lower lobes and perhaps left upper lobe". This could not be confirmed clinically. However, the white blood count by ear-prick was 17,000 per c.mm., suggesting dehydration. A lumbar puncture was carried out to exclude encephalitis; the cerebrospinal fluid was normal. Urine obtained by catheterisation contained salicylate.

The parents first denied giving any medication, but finally admitted giving half a 5-grain aspirin tablet three-hourly for the past three days. They had not liked to admit home treatment.

An electrocardiogram (E.C.G.) showed some flattening of the T waves and from past experience a low serum-potassium was suspected. Peritoneal dialysis was carried out promptly using a rubber catheter to avoid seepage. Bottles of lactated Hartman's solution, with 5% dextrose added to alternate bottles were used. It was realised that the blood-glucose might be reduced too much if large quantities of dextrose-free fluids were given.

During four and a half hours of dialysis, only 66 mg. of salicylate was removed in 2·77 litres of dialysate, with concentrations ranging between 3·5 and 1·7 mg. per 100 ml. However the secretion of urine began shortly after the start of dialysis and concentrations of between 33·6 and 21·1 mg. of salicylate per 100 ml. persisted in urine for the next twenty-four hours. As in the previous case the temperature fell abruptly during dialysis once sweating began.

Though no clinical change was noted in the initial thirty minutes of dialysis, there was a gradual return to full consciousness over the next three hours. Dialysis was ended when respirations fell to normal, and recovery was uninterrupted.

Case 3.—A woman, aged 21, ate about sixty 5-grain aspirin tablets after a combat with an alcoholic husband. When admitted ten hours later she was irrational, breathing stertorously at 45 per minute, and apparently hysterical. The skin was dry, temperature 101°F, pulse 100 per minute, and the serum-salicylate was 73·6 mg. per 100 ml.

No urine could be obtained by catheterisation and semi-coma steadily developed. A serum-ionogram showed sodium 148 mEq., potassium 2·8 mEq., bicarbonate 15 mEq., chloride 103 mEq. An E.C.G. showed flattening of the T waves. As the salicylate concentration was now at a lethal level it was decided to use peritoneal dialysis immediately and later to set up the artificial kidney if this still appeared necessary.

As we now appreciated the importance of potassium depletion, we began with 1 litre of lactated Hartman's solution containing an extra 40 mEq. of potassium.

The patient became excited and complained of pain in the abdomen, but lapsed into semi-coma after a few minutes. Thereafter 14 litres of Hartman's solution were used, with 5% dextrose in alternate litres, over the following three hours. Concurrently an intravenous drip of 0·16 *M* sodium lactate was given for forty-eight hours to provide an excess of available base until the urine was free from salicylate. There was no appreciable change for an hour, then breathing became less laboured, and sweating resumed with prompt remission of the pyrexia. After three hours full consciousness returned and respirations fell to 28 per minute. The total salicylate-content of the dialysate was 640 mg. with concentrations up to 4·8 mg. per 100 ml. A copious diuresis began during dialysis and 3956 mg. of salicylate was recovered in the urine over the next two days (see table).

BIOCHEMICAL SUMMARY

Serum electrolytes (mEq. per litre)	Na	K	HCO_3	Cl	Salicylate (mg. per 100 ml.)	Urine salicylate output (mg.)
On admission ..	148	2·8	15	103	73·6	..
8 hours after dialysis	133	2·0	21·5	103	55·7	2329
34 hours after dialysis	147	2·5	33·6	97·2	9·3	1487
58 hours after dialysis	150	4·2	27·3	112	0	140

Twelve hours after dialysis we became anxious because the patient was mildly drowsy and the blood-salicylate level was 55·7 mg. per 100 ml. However, sweating was free, urinary output of salicylate was high and the respirations were 25 per minute. Her improvement was rapid and our fears vanished during the day. Convalescence was uneventful, apart from the appearance of occult blood in the fæces on the third day.

Discussion

By chance we saw three cases of salicylate intoxication within a few weeks, and we were able to apply successively the lessons learnt from each. In adults with uræmia caused by acute renal tubular necrosis we had used a Kolff artificial kidney with considerable success. From previous experience of salicylate intoxication in children we realised that apparent correction of serum-electrolyte abnormalities, especially serious potassium deficiency, did not ensure survival. We had therefore decided to use the artificial kidney, but faced with desperately ill small children and with the need for speed and simplicity we substituted peritoneal dialysis, using the modification described by Kolff (1955).

Later we discovered that a very careful study of treatment of experimental salicylate intoxication in dogs had been made by Etteldorf et al. (1960) using intermittent peritoneal dialysis. They showed that simple electrolyte solutions used as dialysates were relatively inefficient in removing salicylate from the body, when compared with those containing albumin. Salicylate clearance increased in proportion to the concentration of albumin used. We were unaware at the time that peritoneal dialysis had not been reported in human salicylate intoxication.

Doolan et al. (1959) in a clinical evaluation of intermittent peritoneal lavage mentions incidentally that a significant amount of salicylate was present in the lavage fluid of one of their uræmic patients. They comment that "although no comparative studies have been performed, it seems unlikely that the rate of removal of aspirin, certain barbiturates, bromides or thiocyanate by intermittent peritoneal lavage would approach the rates which have been obtained with the artificial kidney".

Some biochemical lessons may be learnt from our experience. In our three cases there was an evident and serious depletion of available base for enhancement of excretion of salicylate as conjugated glycuronide in the urine, and for the production of sweat. All patients showed severe dehydration with dry skin, absent perspiration (which returned shortly after treatment was started), and pyrexia (which dropped abruptly when base was made available in quantity and sweating began again). The oliguria was abruptly replaced by a diuresis which removed very large quantities of salicylate, in contrast to the relatively small amounts which appeared in the dialysing fluid. All three cases showed either direct or presumptive evidence of a concurrent and dangerous potassium depletion. This was most evident in case 3 (see table) where despite the provision of large amounts of potassium in the dialysing fluid, and in orange juice by mouth during recovery, the levels did

not reach the normal range until more than two days later. Robin et al. (1959) have shown that this is a feature of salicylate intoxication and is probably due to direct salicylate effect on the excretion of potassium by the renal tubules.

On admission case 3 showed an apparently normal serum-sodium, but eight hours after dialysis despite the provision of considerable quantities of sodium-containing fluids the serum level was 133 mEq. per litre. The total body-sodium is probably greatly depleted and this may be masked by the extent of the dehydration.

Almost every physician, who has encountered a number of these cases, stresses that " some patients poisoned by salicylates will die whatever is done " (*Lancet* 1960b). The complex actions of salicylates, which are not completely understood, appear to account for this. Segar and Holliday (1958) have pointed out these poorly understood and paradoxical effects of salicylates. For example, salicylate increases total body-heat production and yet is antipyretic in usual doses. However, the increased sweating which produces the antipyretic effect ends when the total available body-base is depleted and pyrexia then occurs, adding to the mimicry of acute infection, especially when accompanied by a leucocytosis induced by dehydration. The dehydration is then worsened by the dyspnœa. The cause of death in these patients is not clearly understood. Though it is known that hyperpnœa is one of the most valuable warning signs of salicylism, it appears to be produced by a number of factors acting in a set sequence. Initially there is direct stimulation of the respiratory centre, and the blood-pH shows a respiratory alkalosis, which probably enhances the renal excretion of base. This is followed by a metabolic acidosis, partly due to the acidity of aspirin and partly to an increase in unidentified lactate-like bodies, presumably derived from the over-exertion of the respiratory muscles. In small children ketone bodies from starvation play a minor part. Though intermittent 10% carbon dioxide and incomplete neuro-muscular block have both been ineffective, curarisation, and control of the respiratory rate by intermittent positive-pressure respiration have been life-saving by breaking the self-perpetuating metabolic acidosis (Freier et al. 1957).

Besides these important and severe blood-pH shifts there is a strong suspicion that some cases die from severe potassium loss (Robin et al. 1959).

It has been suggested that a plasma salicylate of 40 mg. per 100 ml. is the critical level at which urgent treatment should be carried out (Rentsch et al. 1959). While this may be so it would still seem more important to provide plenty of available base for excretion of the salicylate in the urine.

We have not been able to lay down criteria for the use of this form of treatment, but have been guided by clinical experience, and have instituted dialysis in cases in which we felt that the patient would probably die in a matter of hours even although treated by intravenous 0·16 *M* molar lactate.

The clinical state of case 1 forbade any thought of a prolonged procedure such as replacement-transfusion. In any event, we now feel that the most effective way of allowing the patient to select his own electrolytes in quantity is by peritoneal dialysis.

It may well be a fallacy that gastric lavage is useless after the first few hours, for both acetyl and methyl salicylates are said " to remain in the stomach many hours before absorption and it is hardly ever too late to try to remove them " (*Lancet* 1960a). Garvie (1960) points out, however, that this may lead to pulmonary blockade by regurgitation and aspiration.

In addition, in a series of fifty eight cases of salicylate poisoning reported by us elsewhere (Crichton and Elliott 1960), we have noted that the most serious were those due to therapeutic poisoning. The drug had been administered over a period of several days and often twenty-four hours or so had elapsed between the last dose and the time of diagnosis. This appears to be true in most other large series for example that of Segar and Holliday (1958).

In retrospect we had hoped to wash out the salicylates by dialysis, but we believe that we accomplished more by providing available base as a vehicle for enhancement of renal excretion of conjugated glycuronide.

Summary

Three cases of late salicylate intoxication are described in which peritoneal dialysis proved an effective form of treatment. This procedure was originally undertaken to remove salicylate directly, but was more beneficial in supplying large quantities of available base, including potassium, which had already been seriously depleted, presumably by earlier renal salicylate-excretion.

Though peritoneal dialysis in experimental salicylate intoxication of dogs has been studied, we are not aware of any reports of its clinical use in humans.

We are grateful to Dr. George Miller, Calgary Associate Clinic, for carrying out the surgery in the peritoneal dialyses.

REFERENCES

Crichton, J. U., Elliott, G. B. (1960) *Canad. med. Ass. J.* (in the press).
Doolan, P. D., Murphy, W. P. Wiggins, R. A., Carter, N. W., Cooper, W. C., Watten, R. H., Alpen, E. L. (1959) *Amer. J. Med.* **26**, 831.
Etteldorf, J. N., Montalvo, J. M., Kaplan, S., Sheffield, J. A. (1960) *J. Pediat.* **56**, 1.
Freier, S., Neal, B. W., Nisbet, H. I. A., Rees, G. J., Wilson F. (1957) *Brit. med. J.* i, 1333.
Garvie, J. M. (1960) *Lancet*, i, 1071.
Kolff, W. J. (1955) *Med. Clin. N. Amer.* **39**, 1.
Lancet (1960a) i, 910.
— (1960b) i, 1071.
Rentsch, J. B., Bradley, A., Marsh, S. B. (1959) *A.M.A. J. Dis. Child.* **98**, 778.
Robin, E. D., Davis, R. P., Rees, S. B. (1959) *Amer. J. Med.* **26**, 869.
Segar, W. E., Holliday, M. A. (1958) *New Engl. Med. J.* **259**, 1191.

TREATMENT OF URTICARIA AND QUINCKE'S ŒDEMA WITH A SYNTHETIC ANTIMALARIAL DRUG: AMODIAQUINE

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THIS work originated in observations on a patient who used to have urticaria whenever she was exposed to sunlight. One summer, when she was in Corsica, this did not happen. A possible reason was that, throughout her visit to the island, she was taking amodiaquine daily as a prophylactic against malaria.

Such an effect had been noted previously with amidodiaquine (Sidi et al. 1959) and also with chloroquine (Artom 1959) and mepacrine (Cahn et al. 1954). That amodiaquine and other antimalarial drugs have therapeutic value in certain dermatoses—other than collagenoses—has been reported by the authors just cited and also by Benda and Miravet (1958), Gueorguieff and Badekoff (1958), Meyer (1958), Meyer (1958), and Sidi

et al. (1960). Some experimental work has demonstrated their anti-allergic action (Benda and Miravet 1958, Gueorguieff and Badekoff 1958).

The Present Series

These observations have led us to use amodiaquine regularly in the treatment of obstinate urticaria. Of the 22 cases reported here, some were associated with Quincke's œdema. The condition had lasted for periods ranging from six months to several years and had resisted anti-histamine therapy. The patients were mostly young adults (age-range 20–60 years, average 35), and 13 were men.

Amodiaquine Alone

In 12 cases amodiaquine was given alone, in doses of 200–400 mg. daily during the first week and 200 or 100 mg. daily during the second, third, and fourth. Treatment was interrupted after four weeks, or maintained with low doses (100–200 mg. weekly).

In 4 cases we had no response. Here are two examples:

Case 1.—Madame A., aged 35, had had Quincke's œdema and urticaria for five years, and amodiaquine (200 mg. daily) brought no improvement. Amœbiasis being suspected and proved, she was treated with ' Diphetarsone ', and all symptoms disappeared.

Case 2.—Monsieur B., aged 27, had had urticaria with œdema and localised pruritus (Lewis' syndrome) for five years. He got no benefit from amodiaquine either alone or with an anti-histamine. Laboratory examinations showed an increase in β-lipoproteins and he improved after heparin therapy with a diet low in fats.

The results have been excellent in 4 patients and good in 4. The urticaria was evoked in 2 by sunlight and in 2 by cold:

Case 3.—Every winter for five years Monsieur C., a policeman, has had generalised urticaria and facial œdema when he is exposed to cold or when he washes with cold water. Corticosteroid therapy and anti-histamine therapy has given no result. Ten days after he began to take amodiaquine (200 mg. daily for fifteen days) allergic manifestations disappeared. The treatment was continued throughout the winter with 400 mg. weekly.

In 2 other patients allergy to food has been recognised. Removal of the allergen from the diet has brought moderate improvement, but amodiaquine has done more good.

Case 4.—Monsieur D. aged 42. Daily attacks of urticaria and Quincke's œdema for one year. Found allergic to wine, grape juice, crustacea, fish, and sea-molluscs (mussels, oysters), absorption of which results in intense urticaria. Moreover, the patient is sensitised to the toothpaste he normally uses. Removal of these allergens lessens the attacks, but they do not disappear. After eight months' amodiaquine therapy (200 mg. twice weekly) the attacks are less frequent and less intense. Amodiaquine does not prevent the attack when an allergen (wine, for instance) is absorbed.

Finally, in 2 other patients, men of fifty with urticaria of unknown origin, amodiaquine has given satisfactory results:

Case 5.—Dr. E., a surgeon, had had very intense urticaria for fifteen years. Corticosteroids and antihistamines had been ineffective. Amodiaquine (200 mg. daily) caused considerable improvement. After three months' treatment, some attacks occur but they are very much lessened.

Combined Treatment

In 10 other patients amodiaquine was given either with anti-histamines (7 cases) or with antibiotics (3 cases), both of which had proved ineffective by themselves. We have had 4 failures: no response in 3, and aggravation in 1.

Of the 6 successful cases, the treatment had to be interrupted in 2 because of side-effects (nausea, vomiting, diarrhœa).

In 3 cases of intractable urticaria, antibiotics had been used on account of an infectious syndrome, pointed to by increase of erythrocyte-sedimentation time and of polymorphonuclear leucocytes (10,000 to 15,600). Amodiaquine with tetracycline and nystatin has given good results:

Case 6.—Monsieur G., aged 22, had urticaria attacks with Quincke's œdema every winter. The onset was at 6 months, immediately after anti-diphtheria vaccination. Other remedies having failed, the patient was given tetracycline (500 mg. daily) and nystatin (500,000 u. daily) with amodiaquine (200 mg. daily). After ten days the attacks disappeared. After thirty days antibiotic therapy was interrupted but amodiaquine was maintained (100 mg. daily). After sixty days all therapy was stopped and no urticaria attack has been observed since.

(In 2 cases of asthma controlled by deltacortisone 10 mg. daily, amodiaquine did not improve the quality of result or allow the dose of corticosteroid to be reduced.)

Commentary

In 22 patients with intractable urticaria, amodiaquine was used alone (12 patients), or with anti-histaminics (7 patients), or with antibiotics (3 patients). It proved very effective in 14 cases—2 of sun urticaria, 2 of cold urticaria, 2 of digestive or food urticaria, 3 of infectious urticaria (amodiaquine associated with tetracycline), and 5 of undetermined urticaria.

In 3, despite good results, amodiaquine treatment had to be discontinued because of digestive side-effects.

Among the failures are a case of parasitic origin (chronic amœbiasis) and one of physical origin (mechanical irritation of skin). Consequently we do not think amodiaquine acts as blocking factor of the antigen. Maybe, thanks to photo-protection, it inhibits formation of an autoantigen in the cases of sun urticaria. But the action of amodiaquine is unknown, though from a strictly clinical point of view we can say that it seems to be anti-allergic. Nor can we give any therapeutic schedule: all we can say is that initial daily doses of 200 mg. maintained for fifteen to thirty days seem to be satisfactory.

The benefit, when there is any, appears during the first ten days of treatment. It may continue after treatment stops; or sometimes a maintenance therapy with small doses (200 mg. weekly) is required. Undesirable side-effects are infrequent—in our series digestive disturbances in 2 patients, aggravation in 1, and asthenia in 2. The blood picture is unchanged. However, as some incidents or accidents have been recorded (Meyer 1958, Artom 1959, Sidi et al. 1960) it is necessary to be careful and, in cases of protracted therapy, to examine the blood every second month.

Summary

Of 22 patients with urticaria, amodiaquine, in an average dose of 200 mg. daily, gave good results in 14.

This treatment may be associated with antihistaminics or with antibiotics.

Side-effects are uncommon but should be borne in mind.

REFERENCES

Artom, M. (1959) *Minerva derm.* **34**, suppl. 1, p. 331.
Benda, R., Miravet, L. F. (1958) *Bull. Soc. med. Hôp. Paris*, **74**, 614.
Cahn, M. M., Levy, E. J., Shaffer, B. (1954) *J. invest. derm.* **22**, 93.
— — — (1956) *ibid.* **26**, 201.
— — — (1958) *A.M.A. Arch. Derm.* **78**, 245.
Gueorguieff, G., Badekoff, B. (1958) *III Congr. Int. Allergologie.* Paris.
Meyer, J. (1958) *Concours méd.* **80**, 2435.
Meyer, L. (1958) *Excerpta med. Amst.*
Sidi, E., Hincky, M., Gervais, A. (1959) *Sem. Hôp. Paris*, **35**, 1549.
— Reinberg, A., Hincky, M. (1960) *Pr. méd.* **68**, 833.

CHROMOSOMAL TRISOMY ASSOCIATED WITH THE STURGE-WEBER SYNDROME

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A SURPRISINGLY large number of aneuploid conditions have been reported in man in association with particular congenital defects. This applies to both the autosomes and the sex chromosomes. The known cases of sex-chromosome aneuploidy have been recently summarised by Jacobs et al. (1960) and Hayward (1960). These include monosomic and polysomic conditions. All known autosomal aneuploids are trisomics.

The first such occurrence was shown in conjunction with mongolism (Lejeune et al. 1959, Jacobs et al. 1959, Böök et al. 1959); more recently two additional cases have been described in children exhibiting multiple congenital defects (Edwards et al. 1960, Patau et al. 1960). Perhaps the most interesting report on autosomal trisomy is that of Fraccaro et al. (1960) who have found a trisomic condition in the apparently normal father of a mongol child. These four examples are all trisomic for different autosomes (see table). Our case provides a fifth distinct human male trisomic—in this instance associated with the Sturge-Weber syndrome.

A SUMMARY OF HUMAN AUTOSOMAL TRISOMIC CONDITIONS

Clinical condition	Sex	Trisomic chromosome no.	Reference
Mongolism	M & F	21	Lejeune et al. (1959), Böök et al. (1959), Jacobs et al. (1959)
Cerebral defect, simian creases, trigger thumbs, polydactyly, capillary hæmangiomata, hare-lip, cleft palate, apparent anophthalmia, heart defect	F	15	Patau et al. (1960)
Peculiar facies, webbed neck, heart defect, neonatal hepatitis	F	17	Edwards et al. (1960)
Normal	M	19	Fraccaro et al. (1960)
Sturge-Weber syndrome ..	M	22	Present paper

Case-report

The patient, a boy aged 3 years 10 months, has lived in a residential nursery since the age of 14 months. His mother died, aged 32, shortly after his birth. His father and two siblings are healthy and there is no relevant family history. Before his admission to the nursery he had frequent convulsions but since then phenobarbitone has completely controlled them. Gross mental retardation was present then and little progress has occurred since.

Present state.—His general physical development is average (weight 35 lb. (16 kg.), height 38 in. (97 cm.) but his head circumference is only 18¾ in. (48 cm.). He shows gross mental retardation with hyperkinesis: locomotor abilities are at 12-month level on the Griffiths scale, while other abilities (personal-social, hearing and speech, eye and hand, and performance) are at 6-month level. A "port-wine" nævus covers the distribution of the ophthalmic and maxillary divisions of the right trigeminal nerve. There is buphthalmos of the right eye (iridencleisis has been performed). His face is not suggestive of mongolism (fig. 1). Mild left hemiparesis is present; the left calf is thinner than the right, the left arm is used less well than the right, and the left-arm reflexes are exaggerated.

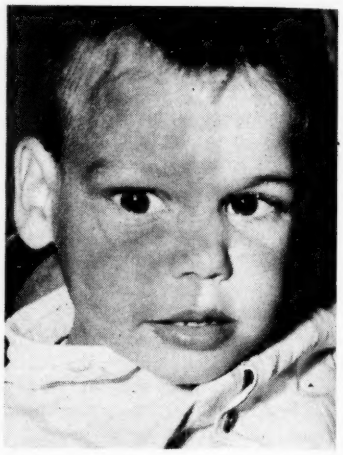

Fig. 1—The patient, showing the extent of the facial nævus and the right buphthalmos.

Investigations

X-ray of skull.—The skull is smaller on the right. There is extensive calcification in the right parieto-occipital region, with the gyral distribution typical of the Sturge-Weber syndrome (fig. 2).

Electroencephalogram (after quinalbarbitone).—There is much less barbiturate fast activity over the right posterior region than over the left, and the slow sleep-activity is also less marked over the right parieto-occipital region than over the corresponding region on the left.

X-ray of pelvis.—The iliac index is 76° (the normal range for male babies is 68°–97° [Caffey and Ross 1956]). It is not known whether this finding has any significance after the 1st year of life; but, if the method is applicable later in life, the result in this child is evidence against mongolism (Dr. Roy Astley).

X-ray of heart.—Within normal limits.

Analysis of prints of palms, soles, and fingers.—Not suggestive of mongolism (Prof. L. S. Penrose).

Cytological Observations

Iliac-marrow punctures were taken from both sides of the body and short-term cultures established. These were subsequently treated by a modification of the standard method described by Ford et al. (1958). Details of this may be found in Hayward (1960).

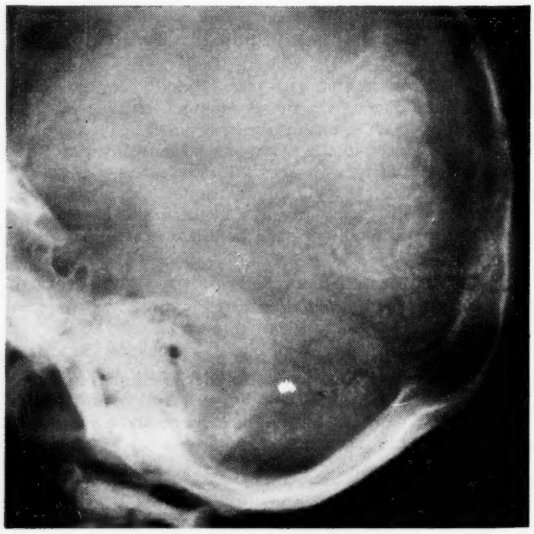

Fig. 2—Lateral radiograph of the skull, showing the "double-contoured" gyral calcification typical of the syndrome.

Chromosome counts on unbroken well-spread cells were:

Chromosome no.	Number of cells counted	
	Right side	Left side
47	58	30
Polyploid	5	1
Total	63	31

Thirty-six cells were selected for detailed analysis and in these the sex-chromosome constitution was XY. In all these cells six small acrocentric chromosomes were found as compared with five in the normal male (fig. 3). Identification of the extra chromosome was difficult by size alone because of the similarity between pairs 21 and 22. It depended, therefore, on the presence or absence of satellites. In none of the cells were there more than two of the small acrocentric chromosomes with satellites. This means that the extra chromosome is probably no. 22 (fig. 4), and not no. 21, the trisomy of which is associated with mongolism (Lejeune et al. 1959). This is supported by the clinical data, for none of the signs are those of mongolism.

Discussion

This is a typical case of the Sturge-Weber syndrome, with no other evident lesions. It is at first sight surprising that an apparently localised, although gross, disorder should be associated with an additional autosomal chromosome, for with one exception the other patients in whom autosomal trisomy has been found have had widespread abnormalities involving several systems (see table). There is, however, pathological evidence that the abnormalities in this syndrome are not as localised as they appear to be. Wohlwill and Yakovlev (1957) in a careful histological study of four cases, demonstrated angiomata in the lung, ovary, intestine, pituitary, choroid plexus, and the meninges, as well as in the skin of the face. In addition, there were heterotopic groups of nerve-cells, scattered throughout the nervous system, apparently the result of failure of migration, and these groups of cells were unrelated to the angiomatous malformations. The gasserian ganglion on the side of the facial nævus was abnormal in two cases. There is, therefore, evidence of widespread dysplasia, affecting both ectodermal and mesodermal structures. Nevertheless the syndrome does not exhibit the wide spectrum of abnormalities seen in mongolism, and in the cases of Edwards et al. (1960) and Patau et al. (1960). It is of interest that the case described by Patau et al. had multiple hæmangiomata, and it was this which prompted chromosome-study of our patient. Angiomatous malformations are associated with artificially induced aneuploids in salamanders (Fankhauser and Humphrey 1950).

There are few recorded instances of autosomal polysomy in animals. Most of these occur in *Drosophila spp.*: thus in *D. melanogaster*, individuals monosomic (haplo 4) and trisomic (triplo 4) for chromosome no. 4 are hardly distinguishable from normal individuals. Interestingly, however, flies tetrasomic for chromosome no. 4 are inviable. Viable autosomal trisomics also occur in *D. subobscura* (Philip et al. 1944). All of these conditions are known only from flies bred in culture. Callan (1941) has described a single individual, trisomic for the third largest autosome, in a wild population of *Mecostethus grossus*.

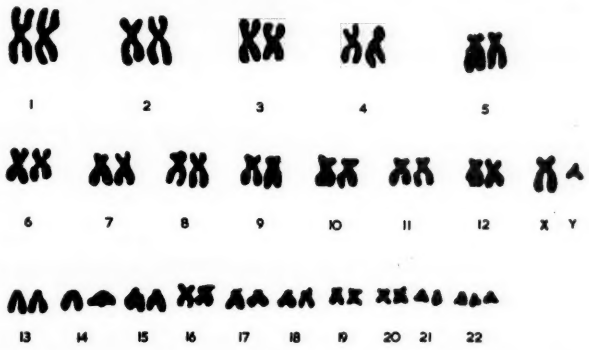

Fig. 4—Chromosomes arranged in pairs showing the trisomy for no. 22.

As polysomic types are apparently rare, the recent discoveries of at least five human autosomal trisomics may seem surprising. It would, however, be even more surprising if this reflected a genuine difference between man and other animals. The more probable reason for this discrepancy is that in man studies have been confined to phenotypically abnormal specimens selected from large populations. No comparable search has been made in other species. Indeed it is possible that in species other than man these polysomic individuals would not survive to a stage where such an examination could be carried out.

In any organism trisomy results from chromosome non-disjunction. This may occur at mitosis or meiosis.

As far as the results of mitotic non-disjunction are concerned one can distinguish that type which occurs during early cleavage divisions of a developing embryo from that arising during the premeiotic mitosis in an adult body. The first type should lead to somatic autosomal mosaicism: the second to the production of aneuploid meiotic cells whose behaviour parallels that of cells in which non-disjunction occurs during meiosis. In both cases the final result is the same—namely, the formation of unbalanced gametes. The possible causal mechanisms which determine mitotic non-disjunction have recently been dealt with in detail elsewhere (Hayward 1960).

Non-disjunction at meiosis may occur during first or second division. Since meiosis II is effectively a haploid mitosis the mechanism and consequences of non-disjunction during this division are essentially mitotic in character and, presumably, similar causal mechanisms operate.

Meiotic non-disjunction at the first division may depend upon three conditions the consequences of which are indis-

Fig. 3—Mitotic metaphase in a bone-marrow cell. 2n=47. (×2500.)

tinguishable: (1) failure of bivalent formation; (2) failure of the homologues of a normal bivalent to disjoin at first anaphase; and (3) irregular segregation of the components of a multivalent in a numerical hybrid or of a multiple configuration in an interchange hybrid (cf. Darlington 1937).

(2) and (3) require no further consideration. But failure of bivalent formation may arise in one of three ways: (*a*) as a result of non-homology between the chromosome pair or pairs concerned; (*b*) as a result of asynapsis (i.e., failure of pachytene pairing between completely homologous chromosomes); or (*c*) as a result of desynapsis (i.e., failure of chiasma formation following successful pachytene pairing).

The first of these necessarily depends upon genic properties but the cause of both (*b*) and (*c*) may be either genotypic or environmental (cf. Rees 1960); this is also true of both bivalent non-disjunction and irregular segregation at first anaphase.

Which of these causal mechanisms determines the observed results of non-disjunction in our patient is not clear. Nor as yet can we postulate a direct causal relationship between the trisomic condition found and the distinctive phenotype of the Sturge-Weber syndrome. This uncertainty is by no means confined to our case; the same consideration may be applied without qualification to the trisomics described by Edwards et al. (1960) and Patau et al. (1960). In both of these cases it has still to be unambiguously demonstrated that autosomal trisomy is the cause rather than an accompanying phenotypic effect expressed at the nuclear level, or a chance association of events. Indeed only in mongolism is it even possible to suggest a relationship between cause and effect; since no normal complement has yet been found in a mongol, it may be reasonably accepted that the abnormal chromosome condition is causal in the production of the defective phenotype. This whole problem of interpretation in such cases is made more difficult by the discovery of a clinically normal male, trisomic for the 19th autosome, by Fraccaro et al. (1960). Only further studies can clarify the situation in respect of autosomal polysomy in man.

Summary

A case of autosomal trisomy associated with the Sturge-Weber syndrome is described. The extra chromosome is cytomorphologically comparable to the five smallest acrocentric chromosomes found in normal males. Reasons are given for its probable identification as no. 22.

The implications of the trisomy and its relation to the abnormal phenotype are discussed.

Our thanks are due to Prof. K. Mather, Prof. D. V. Hubble, Dr. B. John, and Dr. O. H. Wolff for helpful suggestions; to Dr. K. B. Rogers for performing the bone-marrow biopsies; to Dr. Roy Astley for the radiological investigation; to Prof. L. S. Penrose for his opinion on the palm-prints; and to Dr. C. C. H. Chavasse for cooperating in the investigation of the patient.

REFERENCES

Böök, J. A., Fraccaro, M., Lindsten, G. (1959) *Acta pædiat. Stockh.* **48**, 453.
Callan, H. G. (1941) *J. Hered.* **32**, 296.
Caffey, J., Ross, S. (1956) *Pediatrics, N.Y.* **17**, 642.
Darlington, C. D. (1937) Recent Advances in Cytology. London.
Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., Wolff, O. H. (1960) *Lancet*, i, 787.
Fankhauser, G., Humphrey, R. R. (1950) *J. exp. Zool.* **115**, 207.
Ford, C. E., Jacobs, P. A., Lajtha, L. G. (1958) *Nature, Lond.* **181**, 1565.
Fraccaro, M., Kaijser, K., Lindsten, G. (1960) *Lancet*, i, 724.
Hayward, M. D. (1960) *Heredity* (in the press).
Jacobs, P. A., Baikie, A. G., Court-Brown, W. M., Strong, J. A. (1959) *Lancet*, i, 710.
— Harnden, D. G., Court-Brown, W. M., Goldstein, G., Close, H. G., Macgregor, T. N., Maclean, N., Strong, J. A. (1960) *ibid.* i, 1213.
Lejeune, J., Gautier, M., Turpin, R. (1959) *C.R. Acad. Sci.* **248**, 602.
Patau, K., Smith, D. W., Therman, E., Inhoorn, S. L., Wagner, H. P. (1960) *Lancet*, i, 790.
Philip, U., Rendel, J. M., Spurway, H., Haldane, J. B. S. (1944) *Nature, Lond.* **154**, 260.
Rees, H. (1960) *Bot. Rev.* (in the press).
Wohlwill, F. J., Yakovlev, P. I. (1957) *J. Neuropath.* **16**, 341.

CHRONIC Q FEVER WITH MITRAL-VALVE ENDOCARDITIS

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Q FEVER, like the other rickettsial diseases, may be met with in two forms.

The typical illness is an acute systemic infection of abrupt onset with pyrexia, muscle pains, and headache, often associated with pneumonitis. In most acute infections, however, symptoms are probably either absent or so mild that the nature of the disease is unrecognised. The frequency of these subclinical infections can be estimated only by serological surveys of the normal population. Evans (1956), for example, showed that although about 4% of blood donors in South Wales had specific complement-fixing antibodies for Q fever, only 15 of 2482 consecutive cases of non-bacterial pneumonia were caused by *Rickettsia burneti*.

Rarely, Q fever may take a more chronic course. Little is known of the clinical manifestations of this chronic form, but two cases of endocarditis directly due to *R. burneti* have been described recently (Evans et al. 1959, Robson and Shimmin 1959, Andrews and Marmion 1959). In both cases the patients were shown at necropsy to have grossly damaged aortic valves, rickettsial bodies were found in the lesions, and *R. burneti* was isolated from the aortic valves and the spleen. These findings, in the presence of antibody to both antigenic phases of *R. burneti*, were considered good evidence that the illness was a form of Q fever. In neither case, however, could it be shown that there was pre-existing valvular damage.

This paper describes a patient who presented the features of chronic Q-fever endocarditis superimposed on rheumatic mitral stenosis.

Case-record

The patient, aged 33, a locomotive driver, was first seen in 1951 at the Royal Gwent Hospital, Newport, complaining of slight effort dyspnœa. He had had rheumatic fever four years earlier. The diagnosis of pure mitral stenosis of moderate severity was made. In July, 1955, because of increased effort dyspnœa, he was referred to the Chepstow Chest Unit, for mitral valvotomy. The clinical signs were then those of tight mitral stenosis with a pliant valve, and sinus rhythm. A soft, early diastolic murmur was audible at the pulmonary area. At operation on Nov. 9, 1955, the valve just admitted the tip of the index finger. The valve was partially split with the finger. Considerable improvement in effort tolerance followed the operation, and he was seen as an outpatient at regular intervals.

He remained well until April, 1957, apart from three episodes of "influenza" in January, February, and March, 1957. These lasted two to three weeks and were characterised by moderate pyrexia, malaise, and muscle pains. In April, 1957, after palpitation (due to the onset of atrial fibrillation), and pain in the right hypochondrium, he was admitted to the Royal Gwent Hospital. There was no pyrexia. The liver was two fingerbreadths enlarged but the spleen was not felt.

In November, 1957, he had a further episode of "influenza" and thrombosis of the deep veins of the left calf developed.

In September, 1958, he was readmitted with a history of recent "influenza", followed by pain in the left loin and the hypochondrium. There was slight pyrexia at first. The liver was hardly palpable but the spleen was now slightly enlarged. The left renal area was tender. On discharge twelve days later he was apyrexial.

In November, 1958, he was again admitted because of deterioration in general health. Finger-clubbing was noted. Antistreptolysin O (A.S.O.) titre was 500 units (one week later 200 units).

Treatment with aspirin gr. 15 three times daily was begun as the presence of rheumatic activity was suspected. Shortly after he complained of considerable pain and tenderness in the left hamstrings and left middle finger.

In February, 1959, he again had " influenza ".

In June, 1959, he was readmitted because of increased effort dyspnœa and pain in the right hypochondrium. He complained of recent leg pains and occasional attacks of nocturnal dyspnœa. He had lost 14 lb. in weight during the previous six months. Examination revealed atrial fibrillation and considerable mitral stenosis. The liver was enlarged by three fingerbreadths. The spleen was easily palpable and tender. A mild, intermittent pyrexia was present.

He was transferred to Sully Hospital on July 9, 1959. His general condition was poor and he was thin and orthopnœic. The fingers were grossly clubbed, and there was erythema of the palms and cuticles. The extremities were warm. There were no petechiæ, Osler's nodes, or rash. The pulse-volume was small. The jugular venous-pressure was +6 cm. at 45°. Blood-pressure 110/75 mm. Hg. The heart was moderately enlarged and the right ventricle was prominent. The left ventricle was not palpable. The liver and spleen were enlarged by seven and five fingerbreadths respectively, and were moderately tender and firm.

A chest radiograph showed enlargement of right ventricle and left atrium. The main pulmonary artery was larger than in 1955, and the lung fields showed the pattern of combined venous and arterial hypertension. The electrocardiogram showed atrial fibrillation, right ventricular hypertrophy, and digitalis effect. Temperatures ranged from 98 to 100°F.

Investigations

Urine—trace of albumin. No abnormal deposits. Hæmoglobin 80% (11·7 g.); white blood count (W.B.C.) 7000 per c.mm. (neutrophils 65%, lymphocytes 20%, monocytes 5%); erythrocyte sedimentation-rate (E.S.R.) 27 mm. in one hour (Westergren) (July 10), 29 mm. (Oct. 12). Electrolytes normal. Thymol-turbidity 2·5 units. Künkel 6 units. Alkaline serum-phosphatase 21 King-Armstrong units, serum glutamic oxyacetic transaminase 8 units. Bilirubin 0·5 mg. Plasma-protein 6 g. per 100 ml. (albumin/globulin ratio 3·3). Electrophoretic pattern normal. Blood-urea 45 mg. per 100 ml.; A.S.O. titre 200 units. No occult blood in stools. Venous blood-cultures (6) negative, after prolonged incubation. Arterial blood-cultures (3) negative.

Virus Studies

Q fever	*July 29*	*Sept. 9*	*Sept. 14*
Phase 1	1/256	1/128	1/128
Phase 2	1/256	1/128	1/128
Murine typhus	<1/8	<1/8	<1/8

Complement-fixation tests for influenza A, B, and C, psittacosis-lymphogranuloma, adenovirus, lymphocytic choriomeningitis, tests for *Streptococcus MG*, and cold agglutinins were negative.

These findings suggested a diagnosis of chronic Q fever.

When questioned, the patient denied drinking raw milk, and said he had had no contact with domestic ruminants.

Progress and Treatment

Initially he was treated with strict low-sodium diet, hydrochlorothiazide, digoxin, and oral iron. His jugular venous-pressure fell to normal and he was able to sleep lying fairly flat. On July 26 he developed slight hæmoptysis, severe right pleuritic pain, and an extensive pleural rub. Anticoagulation with phenindione (' Dindevan ') was started on the assumption that he had pulmonary infarction. He continued to have intermittent hepatic pain and at times tenderness was sufficient to suggest hepatic infarction. On Aug. 25, hæmoglobin had fallen to 60% (9·65 g.); W.B.C. 8800 per c.mm.; platelets 110,000 per c.mm. The red cells were slightly hypochromic. The sternal marrow was hyperplastic and normoblastic with many macronormoblasts. The thymol-turbidity and Künkel tests gave a value of 10 and 20 units, respectively.

By Sept. 18 the hæmoglobin had fallen to 48% (7·0 g.); hæmatocrit value 24%; mean corpuscular hæmoglobin concentration 29%; reticulocytes 3%. The orthopnœa had grown worse, and so concentrated cells from two pints of blood were transfused. On Sept. 15, after consideration of the final report of the virus studies, it was decided to start treatment with oxytetracycline (terramycin), 2 g. daily for seven days, followed by erythromycin, and chloramphenicol, 2 g. of each daily. The slight pyrexia soon abated and did not recur. His general condition improved greatly and the hæmoglobin rose rapidly to 88% (12·9 g.). The liver and the spleen decreased in size and became less tender. Inoculation of blood and urine into guineapigs gave negative results.

A second mitral valvotomy was performed on Oct. 29, the administration of erythromycin and chloramphenicol having been continued until then. The pericardium was closely adherent. The pulmonary artery was large and tense, and the aorta small. The left atrium was moderately enlarged with a small appendage. The mitral valve again barely admitted the fingertip. The cusps were fibrotic without palpable regurgitation or calcification. Entry to the left atrium was difficult and after three attempts a moderate split of the mitral valve was achieved with a Dubost dilator. Several hours after the operation, he developed cardiorespiratory failure which failed to respond to the usual measures.

Necropsy

The air passages contained a small amount of viscid mucus. Both lungs were congested, œdematous, brownish in colour, and indurated. There was a small wedge-shaped scar on the diaphragmatic surface of the right lower lobe and a similar scar subpleurally on the left lower lobe.

The heart weighed 500 g. The left atrium was hypertrophied and dilated, as was the right atrium. The right ventricle was considerably hypertrophied. The mitral valve was stenotic and slightly incompetent, and the condition had been only partially relieved by valvotomy. There was a traumatic septal defect consisting of a tear, about 1·5 cm. long, in the interatrial septum. There was a roughened area on the posterior cusp of the mitral valve with some brownish vegetations.

The liver was congested. The spleen was enlarged, weighing 700 g., firm in consistence and dark red in colour.

There was an old healed infarct in the left kidney.

Histology and Bacteriology

The mitral valve was thickened and fibrosed, and in one area there was an organising thrombus on the surface: beneath this there was a collection of inflammatory cells consisting of neutrophils, lymphocytes, and mononuclears. A preparation of this area, stained by Macchiavello's method showed rickettsia-like bodies.

The smaller branches of the pulmonary artery showed the changes of reactive pulmonary hypertension.

Suspensions of the mitral-valve vegetations, spleen, liver, and kidney were inoculated into guineapigs previously shown to be free from antibodies for *R. burneti*. Two animals were used for each specimen. Six weeks after inoculation the animals were bled and their serum tested by complement-fixation. Both guineapigs inoculated with mitral-valve suspension had antibody titres of 1/256 for *R. burneti*, whereas the others were negative. These tests were repeated with identical results.

Discussion

Although Marmion et al. (1953) suggested that chronic Q fever might occur when the specific infection was superimposed on pre-existing heart damage, in neither of the two previous cases of proved Q-fever endocarditis was there good evidence of this. Our patient had been treated for rheumatic fever twelve years before we saw him and had undergone a valvotomy for mitral stenosis eight years later. His infection with Q fever apparently occurred about two years after this.

Any patient with the symptoms of infective endocarditis but with negative blood-cultures should have serum tests for Q fever in addition to guineapig inoculation tests of blood and urine. If cases of infective endocarditis with negative blood-culture are indeed due to chronic Q fever, the commonly advised treatment with penicillin and streptomycin will not prove effective. *R. burneti*, however, is usually sensitive to oxytetracycline and the other broad-spectrum antibiotics, and these are better used in combination. On present evidence, the prognosis in these cases is grave.

Summary

A patient in whom rheumatic mitral stenosis was diagnosed in 1951 had the first of a series of episodes of "influenza" in February, 1957. Features suggestive of infective endocarditis were first noted in September, 1958. Blood-cultures and other investigations were negative, but in September, 1959, serological evidence of chronic Q fever was obtained.

A good therapeutic response followed antibiotic therapy with the broad-spectrum antibiotics.

The patient died after mitral valvotomy. At necropsy, small vegetations were present on the posterior cusp of the mitral valve. Guineapig inoculation of suspensions of the vegetations produced high antibody titres for *R. burneti*, and rickettsia-like organisms were seen in sections of the vegetations.

Chronic Q fever should be suspected in patients with the clinical picture of infective endocarditis and negative blood-cultures. The organism is not sensitive to penicillin or streptomycin.

We wish to thank Dr. E. Graham Jones, Dr. L. R. West, and Mr. T. H. L. Rosser for permission to describe this case. Dr. R. M. E. Seal performed the necropsy and gave much helpful advice.

REFERENCES

Andrews, P. S., Marmion, B. P. (1959) *Brit. med. J.* ii, 983.
Evans, A. D. (1956) *Mon. Bull. Minist. Hlth Lab. Serv.* **15**, 215.
— Powell, D. E. B., Burrell, C. D. (1959) *Lancet*, i, 864.
Marmion, B. P., Stoker, M. G. P., McCoy, J. H., Malloch, R. A., Moore, B. (1953) *ibid.* i, 503.
Robson, A. O., Shimmin, C. D. G. L. (1959) *Brit. med. J.* ii, 980.

PIGMENTED NÆVUS OF NAIL

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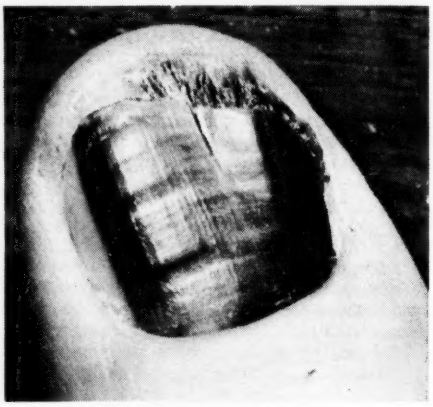
ALTHOUGH the clinical picture of the melanotic whitlow is well known to surgeons and dermatologists, a solitary pigmented (linear) stripe of the fingernail caused by an underlying pigmented nævus may give rise to diagnostic difficulties. Because early diagnosis followed by appropriate surgery carries with it a fairly good prognosis, it is important that this comparatively rare condition should be recognised.

Clinical History

The patient, a Hungarian woman aged 39, was seen in the dermatological department of University College Hospital in October, 1959, with a four-year history of discoloration of her right thumb-nail. This had begun as a pigmented longitudinal stripe which had slowly extended laterally to involve the whole nail except one narrow well-defined segment (see figure). Four months earlier, the nail had cracked longitudinally without any preceding trauma. The whole process had been completely painless, there was no associated inflammation, and the patient asked for advice about treatment because the ragged fissured nail caught in her clothing.



Pigmented nævus of nail.

Her general health was excellent and she had had no serious illnesses or operations.

The right thumbnail was uniformly black except for a segment of normal-coloured nail extending the length of the nail-plate. It was fissured longitudinally and under the free edge of the nail there was a small amount of friable pigmented material. There was no associated inflammation, lymphadenopathy, or hepatomegaly, and there were no other pigmented lesions.

Investigations

Nail-clippings were partially macerated in 20% solution of potassium hydroxide. No fungus could be found on microscopic examination. Abundant dark pigment was seen, both intracellularly and lying free, in the nail. The pigment did not give a positive reaction for iron but was partially decolourised by soaking in hydrogen peroxide, thus indicating that it was melanin.

The probable diagnosis of a junctional pigmented nævus of the nail-bed was made, and under local anæsthesia the nail was avulsed. This revealed a deeply pigmented lesion, and a portion from the nail matrix was excised for histological examination.

The histological appearance was that of a junctional nævus with junctional activity and abundant pigment lying in the dermis. The pigment again proved to be melanin.

Because of the site, and the recent break in the continuity of the nail-plate which indicated either an extension of the nævus or a developing malignant change, it was thought advisable to amputate the terminal phalanx. This was done in December, 1959, and healing was uneventful.

Discussion

The first reference to this condition was made in 1917 by Montgomery who reported a case of a white man, aged 36, who developed a pigmented stripe in his thumb-nail. The stripe was first noted one month after superficial X-ray treatment for eczema of his hands. Although there was no histological evidence to support the diagnosis, Montgomery stated that the most reasonable explanation for the phenomenon was that there was a pigmented nævus, situated in the nail groove, producing pigment in the newly formed nail.

Templeton in 1926 reported a similar case in a Negro woman, aged 28, affecting the left fourth finger and although the presumptive diagnosis of a pigmented nævus was made, there was again no histological confirmation.

Engman et al. (1931) reported a case of a melanotic whitlow which had begun four years previously, as a wide streak extending the length of the nail. Similar cases of malignant melanomata have also been recorded in papers

by Wormack (1927), and Pack and Adair (1939). The latter stated that a pigmented spot under the nail may remain quiescent for a long time as pigmented nævi often do in other parts of the body. Pigmentation had been noted for periods of from two to ten years. They regarded a nævus as being clinically malignant when it broke through the nail.

Pardo-Castello (1941) recognised the longitudinal pigmented bands in nails as deposits of melanin probably secondary to the presence of pigmented nævi in the nail matrix which might have been there since birth. The natural history of the condition was not studied nor was histological evidence provided.

Noble et al. (1952) recorded a case of a pigmented stripe, which had been present for four years, in the fifth left fingernail of a 24-year-old white man. The terminal phalanx of the affected finger was amputated and three years later there was no evidence of local recurrence or of metastasis. The histological diagnosis was that of a benign junctional nævus of the nail matrix.

Unfortunately, few patients come for advice and treatment at the stage when nothing more than a pigmented stripe or spot appears on the nail-plate, and they would probably be reluctant to part with a useful portion of a digit for a seemingly trivial complaint. Amputation, however, does seem to offer a good chance of a cure for a condition which, at a later stage, carries a notoriously bad prognosis. In Negroes, longitudinal bands of melanin pigmentation affecting one or more nails are more common. The pigment is melanin arising from normally functioning melanocytes in the matrix, and the condition, being completely benign, requires no treatment (Pillsbury et al. 1956).

I wish to thank Dr. P. J. Hare for permission to publish this case; Dr. J. Smith, and Dr. Arthur Jarrett for the histological reports; and Mr. David Bailey for carrying out the avulsion and the amputation.

REFERENCES

Engman, M. F., Hook, W. H., Engman, M. F., Jr. (1931) *Arch. Derm. Syph., Chicago*, **23**, 1174.
Montgomery, D. W. (1917) *J. cutan. Dis.* **35**, 99.
Noble, J. F., Ferrin, A., Merandino, K. A., (1952) *Arch. Derm. Syph., Chicago*, **65**, 49.
Pack, G. T., Adair, F. E. (1939) *Surgery*, **5**, 47.
Pardo-Castello, V. (1941) Diseases of the Nails; p. 97. Springfield, Ill. 1941.
Pillsbury, D. M., Shelley, W. B., Kligman, A. M. Dermatology; p. 1022. Philadelphia. 1956.
Templeton, H. J. (1926) *Arch. Derm. Syph., Chicago*, **14**, 533.
Wormack, N. A. (1927) *Arch. Surg.* **15**, 667.

Preliminary Communication

X-RAY-INDUCED CHROMOSOME DAMAGE IN MAN

EVIDENCE that X rays and other types of nuclear and allied radiation cause chromosome damage has been forthcoming for many years, and has accumulated from the study of a variety of plant and animal tissues.[1] From these studies it had been generally assumed that the production of chromosome damage in man was an important mechanism in the establishment of the acute clinical effects of radiation exposure, and possibly also was the cause of such delayed effects as the induction of leukæmia.[2]

TABLE I—CHROMOSOME-COUNT DISTRIBUTIONS: 6 NORMAL SUBJECTS

—	Chromosome counts							Total cells counted
	<44	44	45	46	47	48	>48	
Male ..	..	..	2	32	..	..	..	34
„ ..	..	1	4	29	2	..	..	36
„ ..	..	..	1	30	..	..	..	31
Female ..	..	..	4	39	..	..	..	43
„ ..	..	..	..	30	..	..	..	30
„ ..	..	..	1	30	..	..	..	31
Totals ..	..	1	12	190	2	..	..	205
Percentage	..	0·5	5·8	92·7	1·0	..	..	100·00

As far as direct observations on human tissues are concerned, Fliedner et al.,[3] using simple squash preparations of bone-marrow noted evidence of chromosome "stickiness", clumping of chromosomes, and anaphase bridge-formation in a number of persons accidentally exposed to a mixed neutron/gamma-ray beam. Bender,[4] Puck et al.,[5] and Chu and Giles [6] have studied the effects of radiation exposure in vitro on human tissue-culture preparations. Only recently, however, has it become possible to undertake serial studies of chromosome changes in the directly irradiated human being. This present communication reports the results of such studies in two patients given X-ray treatment for ankylosing spondylitis.

1. Lea, D. E. Actions of Radiations on Living Cells. Cambridge, 1956.
2. Court-Brown, W. M., Doll, R. *in* Modern Trends in Occupational Health. London, 1960.
3. Fliedner, T. M., Cronkite, E. P., Bond, V. P., Rubini, J. R., Andrew, G. *Acta Hæmat.* 1959, **22**, 65.
4. Bender, M. A. *Science*, 1957, **126**, 974.
5. Puck, T. T., Morkovin, D., Marcus, P. I., Cieciura, S. J. *J. exp. Med.* 1957, **106**, 485.
6. Chu, E. N. Y., Giles, N. H. *Genetics*, 1959, **44**, 503.

TECHNICAL CONSIDERATIONS AND RESULTS

The chromosome preparations were made from blood-cultures using an adaptation of the technique of Hungerford et al.[7] the final spreading of the chromosomes being achieved by drying in air. With this technique a count of the chromosomes in 205 cells from six normal subjects showed 190 cells (92·7%) to have 46 chromosomes (table I). This proportion of modal cells did not differ significantly from that in a study of 489 cells from sixteen patients suspected of having chromosome abnormalities but who were found to have apparently normal karyotypes (table II). 449 cells had a count of 46 chromosomes (91·8%) and variations from this modal number are attributed mainly to artefacts arising during preparation. Court-Brown et al.[8] have discussed the causes of variation from the modal number in chromosome counts made on bone-marrow preparations. The improvement in the quality of the preparations, which has followed the introduction of the present technique, is evident from the finding that of 1602 cells from bone-marrow preparations 85% only had a count of 46 chromosomes. A comparison of the count distributions in the pre-exposure blood-samples from the two patients cited

7. Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. *Amer. J. hum. Genet.* 1959, **11**, 215.
8. Court-Brown, W. M., Jacobs, P. A., Doll, R. *Lancet*, 1960, i, 160.

TABLE II—CHROMOSOME-COUNT DISTRIBUTIONS: 16 PATIENTS WITH NORMAL KARYOTYPES

Sex	Diagnosis	Chromosome counts							Total cells counted
		<44	44	45	46	47	48	>48	
M	Arthrogryposis ..	..	1	..	29	..	..	..	30
M	Anophthalmia ..	..	..	..	31	2	..	..	33
F	Spastic diplegia ..	..	..	1	29	..	..	..	30
M	Pelger-Huët anomaly ..	..	..	3	28	..	..	..	31
F	Pelger-Huët anomaly ..	..	..	2	27	1	..	..	30
M	Hydrocephalus ..	..	1	3	26	1	..	..	31
M	Infertility	..	1	1	29	..	..	..	31
M	Infertility	..	..	3	28	..	..	..	31
M	Infertility	..	..	1	29	..	..	..	30
F	Primary amenorrhœa ..	..	..	..	27	1	..	..	28
F	Testicular feminisation	..	..	4	26	1	..	..	31
M	? Marfan's syndrome ..	..	1	1	26	1	1	..	30
M	? Fanconi's anæmia ..	..	..	1	30	..	..	..	31
M	? Mongolism	..	..	2	29	1	..	..	32
F	Primary amenorrhœa ..	..	..	1	28	1	..	..	30
F	Primary amenorrhœa ..	..	..	2	27	1	..	..	30
	Totals	..	4	25	449	10	1	..	489
	Percentage	..	0·9	5·1	91·8	2·0	0·2	..	100·0

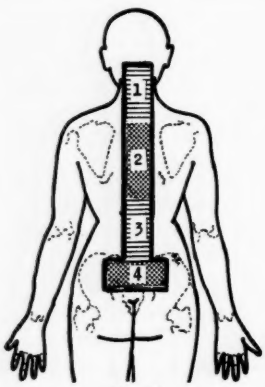


Fig. 1A.

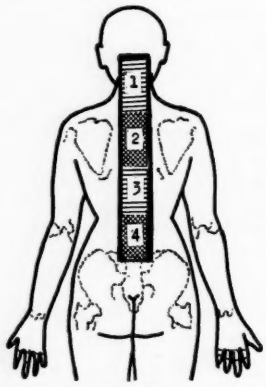


Fig. 1B.

Fig. 1A—Arrangement of X-ray fields and physical characteristics of X-ray beam (Patient A).

Fig. 1B—Arrangement of X-ray fields and physical characteristics of X-ray beam (Patient B.)

kV 250; mA 15; half-value layer 2·7 mm. Cu; focus-skin distance 50 cm.

	Field size (cm.)		*Dose-rate (rads per min.)*	
	A	B	A	B
1	15×10	20×7·5	67·5	66·8
2	20× 7·5	15×7·5	66·8	67·1
3	20× 7·5	15×7·5	66·8	67·1
4	15× 7·5	15×7·5	67·1	67·1

below with those in tables I and II, shows these distributions to be within the normal range of values for the present technique.

The two male patients studied were given X-ray treatment for ankylosing spondylitis. The first patient (A) received treatment to the whole length of his spine and to his sacroiliac joints between July 18 and July 29—a total skin-dose of 1500 rads being given in 10 equal fractions. In the second patient (B), the effect of a single dose of X-rays, 250 rads to the skin over the spinal column alone given on Aug. 10, was studied over a period of ten days by serial blood-cultures. The field arrangements and the physical characteristics of the X-ray beam are shown for both patients in figs. 1A and 1B.

Cells were selected for counting provided that all the small chromosomes (nos. 13 to 22 and the Y chromosome in the Denver classification) were easily identifiable, and in every selected cell these were analysed. It will be seen from tables III and IV that polyploid cells were noted in most of the preparations. These polyploid cells are not included in the chromosome-counts as they can be recognised without a precise count being made. For purposes of comparison, however, an approximate measure of the frequency of polyploids is indicated by the fact that only two were noted during the study of the 694 cells listed in tables I and II. The last technical point to be mentioned is that one of the common effects of radiation is the production of chromosome fragments; and in counting the chromosomes we have adopted the convention of scoring a fragment as a whole chromosome. Thus, a cell with 46 chromosomes and a fragment would be recorded as having 47 chromosomes.

The effect of X-ray exposure on the chromosome constitution of each patient is shown in table III (patient A) and in table IV (patient B).

DISCUSSION

The data from the first patient show clearly that a heavy, accumulated dose of X rays produces considerable chromosome damage. This is shown by significant changes in the count distribution and by a considerable increase in the numbers of cells carrying chromosomes with structural abnormalities. These latter are of many types and no attempt will be made to describe them in this preliminary communication; it is worth noting, however, that chromosome fragments are common and that complex abnormalities such as ring chromosomes and dicentrics are seen (figs. 2 and 3).

The data from the second patient are more informative. A single X-ray exposure was given on Aug. 10 and twenty-four hours later two significant changes had occurred. By then the percentage of cells with 46 chromosomes had fallen from 93 to 72, and that of cells with structurally abnormal chromosomes had risen from 1 to 22. The fall in the modal cells was due to a remarkable increase in the number of cells with 47 chromosomes, which rose from 1% to 21%. During the five days from Aug. 12 until Aug. 17 six blood-cultures were set up but only four were successful, and two of them—Aug. 12 and Aug. 13—were of poor quality. This partial failure may be associated with some effect of irradiation. The unusually low count of modal cells was still present three days after exposure, and on this day the percentage of cells with chromosome structural abnormalities reached a maximum.

TABLE III—CHROMOSOME DATA—PATIENT A

—	Chromosome counts							Total cells counted	Modal cells (%)	Cells with chromosome structural abnormalities (%)		Polyploids
	<44	44	45	46	47	48	>48			Modal cells	All cells	
July 18 (pre-exposure) ..	1	..	3	44	2	..	..	50	88	0	2	0
July 22	1	1	7	33	6	2	..	50	66	18	40	0
Aug. 2	..	..	7	37	2	1	3	50	74	19	34	11
Aug. 12	1	..	5	34	7	1	2	50	68	9	32	7
Aug. 18	..	..	5	43	1	1	..	50	86	16	18	3

The changes in the proportion of modal and non-modal cells found on July 22, Aug. 2, and Aug. 12 by comparison with the proportion in the control blood of July 18 are highly significant. The values of χ^2 and P (n = 1) are respectively 22·92 and <0·001; 9·29 and <0·01; and 18·96 and <0·001.

TABLE IV—CHROMOSOME DATA—PATIENT B

—	Chromosome counts							Total cells counted	Modal cells (%)	Cells with chromosome structural abnormalities (%)		Polyploids
	<44	44	45	46	47	48	>48			Modal cells	All cells	
Aug. 10 (pre-exposure) ..	..	..	5	93	1	..	1	100	93	0	1	1
Aug. 11	1	1	4	72	21	1	..	100	72	7	22	11
Aug. 12	1	..	3	27	4	..	..	35	77	18	23	1
Aug. 13	..	..	1	19	2	3	2	27	70	27	41	0
Aug. 15	..	..	2	90	6	1	1	100	90	11	16	3
Aug. 17	..	..	3	93	2	1	1	100	93	6	11	0
Aug. 19	..	2	3	89	4	..	2	100	89	4	10	6
Aug. 21	..	..	1	90	9	..	..	100	90	2	9	8

The changes in the proportion of modal and non-modal cells found on Aug. 11, Aug. 12, and Aug. 13 by comparison with the proportion in the control blood of Aug. 10, 1960, are highly significant. The values of χ^2 and P (n = 1) are respectively 67·74 and <0·001; 13·52 and <0·001; and 21·24 and <0·001.

Fig. 2—Cell from patient A, with 50 chromosomes, showing ring chromosome (R) and fragments (F).

By the fifth day, however, the percentage of modal cells had returned to within normal limits, and remained so for the rest of the period of observation. The fifth day also marked a decline in the number of cells with structural abnormalities, but even on the last two days of observation these were present in 9 to 10% of the cells.

In both patients unusual numbers of polyploid cells were seen. Perhaps the most striking increase was that occurring twenty-four hours after the X-ray exposure of the second patient. At this time 11 polyploids were noted during the finding and counting of 100 cells with diploid or near-diploid numbers.

Fig. 3—Cell from patient A, with 46 chromosomes, showing one definite dicentric chromosome (D) and a second possible dicentric (D_1).

Findings resembling these have been noted by us in cases of chronic myeloid leukæmia after X-ray treatment. These will be discussed in a later communication.

In conclusion, the data indicate, as might be expected, that X rays readily produce chromosome damage which can be detected in cultures of human blood-cells. Much more work will be necessary to achieve a fuller understanding of the pattern of the changes, particularly the effect of varying such physical parameters as the total dose and the dose-rate. What we have learnt about the extent of the damage produced by a single dose of 250 rads, limited to the skin over the spinal column, gives grounds for hoping that the relationship between radiation dose and the extent of chromosome damage in man may be evaluated by direct observation over a wide range of doses.

We are indebted to Prof. R. McWhirter and his staff for access to patients under their care, and to Miss M. Brunton and Miss G. Woodcock for technical assistance.

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New Inventions

A DEVICE FOR CONTROLLING THE FLOW OF PARENTERAL INFUSIONS

A SMALL, reliable, and inexpensive device has been developed for monitoring the flow of parenterally administered solutions. It alerts the attention of the nurses and also automatically stops the flow when the predetermined volume has passed.

Fig. 1 is a diagram of the apparatus, and fig. 2 represents

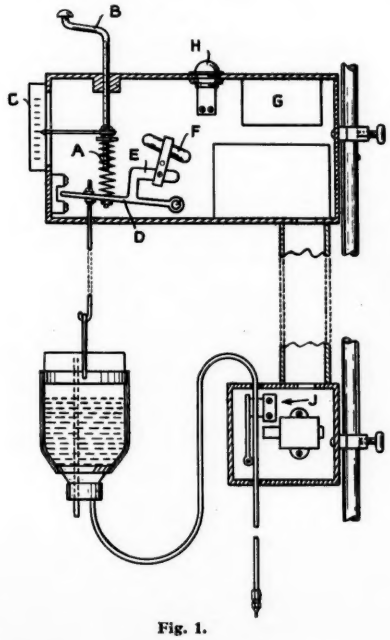

Fig. 1.

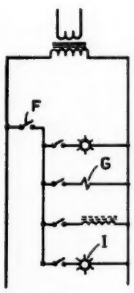

Fig. 2.

the electrical circuits. The tension on the spring (A) is set by a crank (B) which points on a scale (C) calibrated in units of 50 ml. of solution. As the preset volume is consumed, the infusion bottle loses weight and rises. This movement is translated by levers (D and E) into the closing of a mercury switch (F). When the switch closes, the triple-alarm system and the automatic flow cut-off are activated. The alarm comprises a ringing bell (G) and a red flashing light (H) at the bedside, and another flashing light (I) at the nurses' station. The automatic flow cut-off attachment (J) is an electromagnet of the hinge-clapper or solenoid type, which pinches off the plastic tubing through which infusion flows. This cut-off device and the alarms are wired in parallel, each with its own switch, to provide the greatest versatility.

If every 50–100 ml. of infused solution is thus monitored, acute pulmonary œdema, due to inadvertent acceleration of the speed of infusion in patients with compromised cardiac reserve, would be decreased. If the apparatus is set at some point before complete emptying of the infusion bottle, the danger of air-embolism due to positive-pressure fluid administration (e.g., during cardiac catheterisation) would be slight. By alerting attendants before complete consumption of the solution, the device would diminish the frequency of repeated venepunctures due to clotted needles—a constant source of irritation to patients and house-staff alike—and would obviate the necessity for " cut-downs " in patients with inaccessible veins.

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A CONTROL UNIT FOR SUCTION WITH REPEATED RELEASE

HOWEVER elaborate or expensive surgical suction apparatus may be, it is useless if the suction tube becomes blocked. This may happen when the volume to be aspirated is small, as in infants, because tissue surfaces are drawn in by the negative pressure over the open end of the tube. If the suction is constant this fault is unlikely to clear itself.

Repeated manual aspiration by a trained nurse is one solution to the problem, but this is expensive in terms of skilled time. In the United States pumps with an intermittent suction action are widely adopted; and, although these still require supervision, they do save nursing time.

Better results can be expected (except in the pleural cavity) if the suction is briefly and repeatedly alternated with atmospheric pressure. The apparatus here described has been designed to convert instantly any continuous-suction pump to this type of action. It is constructed entirely from standard electrical and electronic components housed in a simple case (fig. 1).

Fig. 2 is a block schematic diagram of the apparatus. The cycle of operation requires that two automatic solenoid valves (SV_1, SV_2) be incorporated in the suction tube, and these are energised in turn to provide suction periods of 20 sec. separated by intervals of 2 sec. During these intervals the distal end of the suction tube is open to the atmosphere. A reservoir, having a volume at least three times that of the collecting bottle, is used in conjunction with the pump. This, together with the long suction period, permits the use of a small pump.

The control circuit is shown in fig. 3. The timing impulses, obtained from the transistor multivibrator (T_1, T_2) are fed to the driver transistors (T_3, T_4), which govern the operation of the solenoid valves. The pilot lamps (L_1, L_2), coloured green and amber respectively, give visual indication of the timing cycle. In the event of lamp failure the operation of the unit is unaffected. The power supply is a basic mains-operated bridge-rectifier circuit, giving an output of 24V and 0·5 amp.

The unit has proved reliable in use, and the nurses like its simplicity of operation.

We are indebted to Mr. Joseph Devlin for the photograph.

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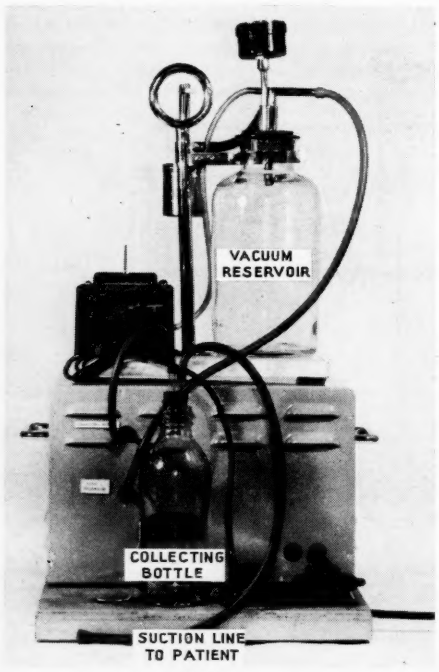

Fig. 1.

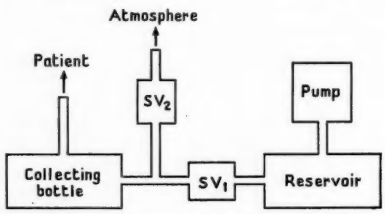

Fig. 2.

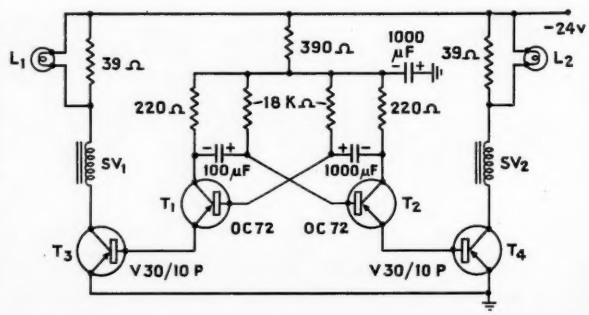

Fig. 3.

Medical Societies

SOCIETY FOR SOCIAL MEDICINE

THE fourth annual meeting of the society was held in Oxford from Sept. 29 to Oct. 1.

Leukæmia

Dr. ALICE STEWART (Oxford) propounded the view that many cases of stem-cell leukæmia in childhood have their origin in an inherited defect. Children in the preleukæmic state (like mongols, who have an exceptionally high risk of developing leukæmia) are especially liable to die of pyogenic infections. Hence both the number of deaths attributed to leukæmia and their age-distribution have been altered by the advent of antibiotics and by the declining incidence of these infections.

Dr. J. A. H. LEE (London) described a " bulge " in the age curve of mortality from leukæmia between the ages of 13 and 19. This is due to a temporary rise in acute myeloid cases, most notable in males, which is evident on both sides of the Atlantic, and can be traced back at least as far as the 1920s.

Dr. F. W. GUNZ (Christchurch, New Zealand) reported on a study now in progress which covers over 80% of leukæmia cases diagnosed throughout New Zealand. Although reporting is relatively incomplete in Maoris, chronic lymphocytic leukæmia is clearly less common in this group than in the population of European origin. Compared with their controls the leukæmia cases showed a clear excess of exposures to radiotherapy and of personal histories of cancer, but at most 7% of all cases could be accounted for in terms of any recognised ætiological factors.

In the discussion questions were raised about recent evidence conflicting with previous reports of an association between childhood malignant neoplasms and antenatal radiography. Dr. RICHARD DOLL (London) said that his own study, relating to leukæmia in children, had not confirmed this association, but that it could not be regarded as disproved.

General Epidemiology

A large body of data collected by the Veterans Administration in the U.S.A. was used by Dr. E. D. ACHESON (Oxford) to demonstrate a rising incidence of multiple sclerosis from south to north, both between and within States, and applying to both white and coloured men as well as to veterans of both world wars. Reasons were given for believing that this gradient did not merely reflect differences in diagnostic standards, and certain climatic variables (severity of winter, rainfall) could also be ruled out. Preliminary analysis of mortality data from the southern hemisphere appeared to confirm the positive correlation between incidence of multiple sclerosis and latitude.

Dr. D. CAMERON and Dr. G. D. FORWELL (Edinburgh) had attempted a complete ascertainment of cases of diagnosed diabetes among the patients in 77 Scottish practices. The overall prevalence was between 4 and 5 per 1000 population. The prevalence estimates paralleled mortality figures in showing an excess of cases among manual workers in the younger adult age-groups, and an excess among non-manual workers at higher ages.

A paper by Dr. DOLL and Dr. R. E. W. FISHER (London) showed how detailed epidemiological analysis, supplemented by chemical study of air samples, had led to the inculpation of an old-fashioned type of retort as responsible for the excess of deaths from lung cancer among gas-retort workers. In studies of this type one should not trust mortality expectations computed from national data to yield a standard appropriate to a selected industrial group, but occupational mortality-rates within the industry could be compared with some confidence.

Pregnancy Hazards

Why do only a small proportion of the second and later rhesus-positive children born to rhesus-negative women develop hæmolytic disease of the newborn? This question was discussed by Dr. E. G. KNOX (Newcastle upon Tyne), whose previous work had shown that maternal-fœtal ABO incompatibility tends to prevent sensitisation of rhesus-negative mothers. Comparison of the obstetric details in a group of sensitising pregnancies with a control group indicated that toxæmia, surgical interference, and placental anomalies were among the factors which might pave the way for rhesus isoimmunisation in a later pregnancy.

Dr. R. G. RECORD (Birmingham) discussed variations in the incidence of anencephalus, which has shown a rising trend in recent years. Though the variables implicated are to some extent confounded with one another, at least four (parity, maternal age, low social class, season of conception) can be shown to have an independent effect.

Psychiatry: Mental Abilities

Dr. J. K. WING (London) had conducted a study of male schizophrenic patients under the age of 60 who had been resident at two London mental hospitals for upwards of two years. Though mental symptoms and most types of ward behaviour showed no significant trend with length of stay in this group, unfavourable attitudes to discharge were commoner in the longer-stay patients. This was interpreted as reflecting a syndrome of " institutionalism ", possibly similar to a syndrome which has been described in other segregated communities.

Six years after their discharge from mental hospital two-thirds of a group of patients were found to be " not ill from a psychiatric point of view ". This favourable outcome was reported by Dr. LILLI STEIN and Dr. W. WARREN (London) in their follow-up study of patients treated in the adolescent unit of the Bethlem Royal Hospital. Relatively young patients (under 14 on admission) did well, as did those with neurotic rather than psychotic or organic disorders, but on an individual basis there was little association between prognosis at discharge and condition at follow-up.

The influence of birth rank and family size on educational selection was discussed by Dr. J. W. B. DOUGLAS (Edinburgh), who produced evidence that the handicapping of later children and children from large families derived from environmental rather than genetic factors. A measure of parental interest in the child, generally higher for children of small families, was found to correlate not only with performance at the ages of 8 and 11 but also with the progress achieved between these ages.

Dr. MERVYN SUSSER and Dr. ZENA STEIN (Manchester) reported on a study of the social distribution of children classed as educationally subnormal. Except when associated with brain damage this condition appeared to occur only in families belonging to what was characterised as a " demotic " —in contradistinction to an " aspirant "—subculture. Data from other studies were adduced in support of the thesis that this type of mental retardation is due to environmental factors.

Reviews of Books

Doctors and Disease in Tudor Times

W. S. C. COPEMAN, O.B.E., F.R.C.P. London: Dawsons. 1960. Pp. 186. 42*s*.

THEON, the mathematician of Alexandria and the last notable philospher of the Graeco-Roman era, died about A.D. 400. A kind of twilight descended on men's minds thereafter, and did not lighten for more than a thousand years. Then, in 1543, two great works appeared, distinguished because they did not merely repeat old dogmas but contained new observations and were based on experimental methods. One was Vesalius's treatise on human anatomy, and the other the *De revolutionibus orbium caelestium* of Copernicus. The Dark Ages were over, and the Renaissance had begun.

In this country, about the same time, the Tudor period began, and within that era Linacre founded the Royal College of Physicians, and Vicary united the Guild of Surgeons with the Barber's Company. John Caius created one of our first medical schools and William Harvey went to study there. The significance of such times for the medical historian needs no

emphasis. Fortunately, they are abundantly documented, for the same era saw the wide development of printing: indeed, the first volume ever printed in these islands, it is said, was a clinical study—von Hutten's subjective account of syphilis. Most medical studies of the period are concerned with some particular aspect of Tudor medicine, and Dr. Copeman's book is remarkable for its breadth.

The first chapters deal with the status of the physician, his education, and the doctrines that he was taught. The succeeding ones describe the diseases which confronted him, and the medicaments and instruments he could deploy against them. A final section discusses public-health practices of the day. Dr. Copeman is clearly well versed in all the ordinary texts, on which his remarks constitute a useful and authoritative commentary. The book contains in addition much information not easily found elsewhere: how, for instance, a " vomit " was prepared by allowing wine to stand in an antimony cup for some days until it had become impregnated with tartar emetic. Dr. Copeman also describes the origin of our national dish of bacon and eggs: and differentiates clearly between a seton and an issue, which is more than most dictionaries do.

Atlas and Manual of Dermatology and Venereology

Prof. W. BURCKHARDT, director of the Municipal Policlinic for Skin and Venereal Diseases, Zürich. Translated and edited by STEPHAN EPSTEIN, M.D. Baltimore: Williams & Wilkins. London: Baillière, Tindall, & Cox. 1960. Pp. 281. 112*s*.

IN an atlas of dermatology which is intended for the practising dermatologist, illustrations of common skin diseases, however excellent, are a waste of money and space; but in an atlas designed for the student or practitioner with limited experience many photographs are needed to illustrate all variants of the commoner skin diseases. The preface to the American edition of Professor Burckhardt's book makes it clear that it is intended for the non-specialist reader, yet the 73 illustrations and 99 colour plates can give only a glimpse of some aspects of each disease mentioned, and some common, as well as not so rare, diseases are not illustrated at all. The illustrations and colour plates, drawn mainly from *Folia Dermatologica*, are of the highest quality; but space could have been saved and used for additional illustrations if the size of some had been reduced.

Undoubtedly it is difficult to select the correct material to include in a textbook of this kind; but some commoner conditions, such as scurvy as a cause of purpura, have been omitted while comparative rarities have been mentioned. The 29 pages on venereal diseases give a clear succinct account of the main problems which may be met in general practice. Dr. Peter Smith has supplied information about medication in Britain. The therapeutic advice given is sound even if some proprietary names may be unfamiliar to British readers.

Report of the First Institute on Clinical Teaching

Editors: HELEN HOFER GEE, JULIUS B. RICHMOND. Evanston, Illinois: Association of American Medical Colleges. 1959. Pp. 233. Cloth $3.00, paper $2.00.

THE 1958 " institute " of the Association of American Medical Colleges was the first of two devoted to clinical teaching. It was organised on similar lines to those held every year since 1953. The main subject was broken down into several topics, and on each of these many factual data were collected from the medical schools by the research division of the Association. The discussions started by the main speakers therefore were based not only on personal opinions and experience but also on a reasonable quantity of relevant facts.

The main subjects were the objectives of clinical teaching; the setting of clinical teaching; the student, the patient, and the teacher; and extramural forces influencing medical education. The last topic included a symposium entitled " Other disciplines look at Medicine ", with papers from a philosopher, an economist, and a behavioural scientist. The report also includes the principal papers on each " topic ", together with the data collected by the research division. It offers the British reader interesting and even provocative views on the aims and methods of clinical teaching, and on the functions of university hospitals. It also provides a reference book on almost every aspect of clinical medical education in the United States and Canada. The types of hospitals and even patients are listed, with details of curricula, forms of experience offered to students, and a sample of staff and student opinion on all these things. The financing of clinical teaching, the methods of control over it exerted by the schools, and the methods of selecting teachers and of appointing clinical staff are also set out, and generally make a very interesting comparison with our own methods.

The quantity of information here is vast and by no means all of it is relevant to Britain, but those responsible in this country for the organisation of clinical teaching will find much that is challenging, though perhaps less that is comforting, for they can hardly fail to note how little authority they have compared with those responsible for teaching in North America. The British clinical teacher whose responsibility is more limited and personal will also find much of interest, and if by chance he is one who knows all there is to know of this complex subject by intuition, inheritance, or other forms of internal revelation, he will be intrigued to find how many teachers exist to whom some quite different convictions have been given, and that there are others who are still searching for some of the answers.

Congenital Malformations (London: J. & A. Churchill. 1960. Pp. 308. 45*s*.).—This book, edited by Dr. G. E. W. Wolstenholme and Miss Cecilia O'Connor, is the text of a notable Ciba Foundation symposium, held in January this year, on the ætiology of congenital malformations, with Prof. W. J. Hamilton in the chair. Prof. Thomas McKeown reports the incidence of malformations in the city of Birmingham over the three years 1950–52, and relates this to the incidence found in other large series. Dr. A. C. Stevenson describes the association of hydramnios, not only with anencephaly and gut obstructions, but with a large variety of malformations. Prof. L. S. Penrose discusses the genetical causes of malformations, and Dr. C. E. Ford describes the recent advances that he and others have made in the recognition of chromosome abnormalities in certain classes of malformed children. Then Dr. T. H. Ingalls gives a general account of environmental agents causing malformations in man. A series of remarkable papers follows showing the variety of chemical agents which may induce fœtal malformations in laboratory animals. These include tumour-inhibiting chemicals, such as the alkylating agent chlorambucil; antimetabolites, such as the folic-acid analogue aminopterin; antibiotics, such as actinomycin D; and even hypervitaminosis A, which, as Prof. A. Giroud reports, will produce in rats and mice malformations very similar to human anencephaly. It should not be long before some of this careful and elegant experimental work finds practical application in antenatal pædiatrics.

The Mechanism of Action of Insulin. (Oxford: Blackwell Scientific Publications. 1960. Pp. 320. 32*s*. 6*d*.).—This volume is a record of a symposium convened in September, 1958, by the British insulin manufacturers in London. Many prominent research-workers from North America and the Continent, as well as from Britain, took part. In his introductory remarks the chairman, Prof. F. G. Young, invited those present to " let their hair down ", and this exhortation contributed to a friendly informality and free speculation which make the book stimulating to read. The subjects discussed ranged more widely than the title of the symposium suggested, and they included the chemistry of insulin, bioassays of insulin, insulin antagonists, the mechanism of the hypoglycæmic action of salicylates, thiol substances and the sulphonylureas, and prediabetes in pregnancy; but even on the subject of the mechanism of action of insulin the text reveals much that is controversial even after the research of nearly forty years. The symposium was a success, and this record, edited by Mr. W. A. Broom and Dr. W. F. Wolff, is valuable as an integation of so many areas of diabetic research related more or less closely to insulin.

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Tranquillisers in Psychiatry

THE *bon mot* describing chlorpromazine as a substance having only side-effects has been conclusively proved wrong: clinical reports from many countries have now confirmed the original observations by DELAY and DENIKER [1] on its value in the treatment of schizophrenia. Concurrently reserpine was shown to have similar indications in psychiatric practice.[2] The era of tranquillisers, a generic term coined to distinguish these drugs from traditional sedatives, has begun: by definition they act on the emotional state without affecting clarity of consciousness. It is a somewhat grandiloquent and not strictly accurate term, but it is probably here to stay.

Many phenothiazine derivatives [3] have been devised by modification of the chemical structure of chlorpromazine; and other supposedly beneficial, though chemically unrelated, drugs, have been marketed for the treatment of mental illness. This abundance of riches for the traditional poor relation of physical disease is welcome; but some of the new compounds have been introduced without full enough clinical experience of them for their therapeutic value and toxicity to be confidently appraised. Since the ætiology of mental disorders is still largely unknown, theoretical consideration or observations on animals form only a tentative basis. In psychiatry even more emphatically than in other branches of medicine, clinical results remain the final arbiter of effectiveness and safety. Enthusiasm seems to be running well ahead of evidence; and it is reported that in 1958 alone the sale of these drugs in the U.S.A. exceeded £70 million.[4]

Chemically the tranquillisers can be divided into three groups: reserpine; the phenothiazine derivatives; and drugs of varied chemical structure, such as meprobamate, benactyzine, and methaminodiazepoxide. Reserpine, although often very effective in the treatment of severely disturbed and overactive patients, has autonomic effects; and it is being gradually replaced in psychiatric practice by phenothiazine derivatives. These differ among themselves in the nature of the side-chain attached to the phenothiazine nucleus: the dimethyl subgroup, including chlorpromazine and promazine, and the piperazine subgroup, comprising perphenazine and trifluoperazine, are the two most important. Thioridazine, which has a thiomethyl radical substituted in position 2 of the phenothiazine nucleus, is in a category by itself. The drugs differ in dosage and toxicity. Among the most dangerous toxic effects are agranulocytosis, hypotension and vascular collapse, increased liability to thrombosis, hepatic dysfunction, convulsions, and depression [5]; these toxic effects are rather commoner with the dimethyl subgroup. Sedation is also commoner with this subgroup, of which chlorpromazine is still the most widely used, and they are therefore preferred in the treatment of conditions characterised by overactivity. Piperazine derivatives, of which trifluoperazine is probably the most widely used, tend to produce motor restlessness and anxiety—symptoms for which American workers have adopted the term akathisia originally applied by SICARD [6] to similar manifestations in post-encephalitic parkinsonism. Extrapyramidal symptoms, a side-effect common to all phenothiazines, appear generally earlier with the piperazine subgroup, which seems particularly effective where delusions are the central feature of the illness. Thioridazine, not as yet widely used in this country, is said to have many of the sedative properties of chlorpromazine, but with fewer side-effects and negligible toxicity.[7]

As regards the third (miscellaneous) group of tranquillisers, opinion is unanimous only about their ineffectiveness in schizophrenia. They are claimed to be useful in a large variety of psychological disorders generally termed neurotic, particularly those in which anxiety is prominent. In this large and ill-defined clinical area the abnormal merges imperceptibly into what has to be regarded as normal. Therapeutic studies should therefore be carefully designed and cautiously judged. Yet the claims made are often based on uncontrolled trials; and in controlled trials [8 9] positive results have either been very modest or totally absent. Most psychiatrists would therefore agree that tranquillisers have proved a failure in the treatment of neuroses.[10] Only time will tell whether methaminodiazepoxide, one of the latest additions to this group, will be more successful than its forerunners. Unfortunately, the reports so far published [11] are uncontrolled and correspondingly less convincing. A fortnight ago Dr. INGRAM and Dr. TIMBURY,[12] impressed by the troublesomeness of side-effects, suggested that meanwhile this drug should be used with circumspection. Correspondence last week [13] and in the present issue shows that, in the experience of others, side-effects have been less common and severe. But on the existing evidence the therapeutic usefulness of this drug cannot be regarded as established; and toxic effects, such as ataxia, dermatitis, and rage reactions,[12] suggest a need for caution.

1. Delay, J., Deniker, P. C.R. Congrès de Psychiatrie et de Neurologie de Langue française. Luxembourg, 1952.
2. Kline, N. S. *Ann. N.Y. Acad. Sci.* 1954, **59**, 107.
3. Rees, L. *Brit. med. J.* Aug. 13, 1960, p. 522.
4. Shaw, E. B., Dermott, R. V., Lee, R., Burbridge, T. N. *Pediatrics*, 1959, **23**, 485.
5. Wortis, J. *Amer. J. Psychiat.* 1960, **115**, 595.
6. Sicard, A. *Pr. méd.* 1923, **23**, 265.
7. Kinross-Wright, J. *J. Amer. med. Ass.* 1959, **170**, 1283.
8. Hargreaves, G. R., Hamilton, M., Roberts, J. M. *J. ment. Sci.* 1958, **104**, 1056.
9. Hinton, J. *J. Neurol. Neurosurg. Psychiat.* 1958, **21**, 301.
10. Laurence, D. R., Pond, D. A. *Brit. med. J.* 1958, i, 700.
11. *Dis. nerv. Syst.* 1959, **21**, suppl. 3.
12. Ingram, I. M., Timbury, G. C. *Lancet*, Oct. 1, 1960, p. 766.
13. Jenner, F. A., Kerry, R. J., Parkin, D. *ibid.* Oct. 8, 1960, p. 816.

Although chemically unrelated, both reserpine and the phenothiazines are effective in the treatment of schizophrenic conditions, and both are liable to produce extrapyramidal symptoms. The frequent association of clinical improvement with drug-induced parkinsonism [14] has led some to regard the two as necessarily linked [15] and has inspired interesting speculations on the pathological basis of schizophrenia. But these two effects are not strictly parallel, and the suppression of extrapyramidal side-effects by drugs does not apparently impair therapeutic efficacy. From the clinical, and possibly the neurophysiological, point of view it nevertheless seems reasonable to group reserpine and the phenothiazines together, separating them from the third group—the tranquillisers pure and simple. Another designation, such as neuroleptic [16] or neuroplegic,[17] might be more appropriate for reserpine and the phenothiazines.

The efficacy of reserpine and the phenothiazines in many acute and some chronic schizophrenic illnesses has raised the question whether they intervene in the abnormal biochemical processes which many believe underlie schizophrenia. Reserpine sedation is generally believed to be related to the depletion of cerebral biogenic amines, in particular serotonin and noradrenaline.[18] The phenothiazines, like biogenic amines, have three carbon straight chains with a terminal nitrogen atom; possibly these drugs compete with the amines for receptors in the central nervous system, thus preventing the actions normally exerted by the amines.[19] The blocking of serotonin and noradrenaline achieved, through different mechanisms, by both reserpine and the phenothiazines may account for their largely similar effects in psychiatric treatment. This relationship of known pharmacological properties to clinical efficacy cannot yet be regarded as established; and a biochemical mythology of mental disorder, based on tempting but largely unsubstantiated speculations, might clearly prove harmful in the long run. But the systematic exploration of hypotheses based on known pharmacological actions, coupled with critical appraisal of drug therapy in clinical practice, may lead to a better understanding of the physiopathology of mental disorder and open the way to its rational treatment.

Heatstroke

THE mode of onset of heatstroke has not been clearly established. The two main issues are whether cessation of sweating precedes or follows hyperpyrexia, and whether circulatory failure is or is not a constant and important feature. One reason for the continuing doubt on these questions is that in heatstroke, which is one of the most urgent of all medical emergencies, treatment has priority over investigation; while the high mortality even with rapidly effective cooling rules out experimental induction of the condition in man. Another reason is that heatstroke is often a catastrophe of sudden and unheralded onset, and not the climax of several days' debility, pyrexia, and diminished sweating.

A hypothesis which bids to answer both the main questions at once has been propounded by GOLD,[1] who has made important observations on the development of heat pyrexia in men exposed in the laboratory to dry heat, some for two hours at 54·5°C (130°F) and others for one hour at 71·1°C (160°F). He has confirmed that exposure to severe heat is accompanied at first by a hyperkinetic circulation and a raised cardiac output, and in several subjects he found considerable rises of pressure in a forearm vein. He observed a quantitative correlation between the rise in venous pressure and what he describes as effective body-heat storage, which appears to be a partly theoretical assessment of heat gained by the body despite maximum operation of heat-dissipating mechanisms. Each subject was removed from the hot chamber when collapse was judged to be imminent, on the basis of abnormal sensations such as light-headedness, and of a facial colour change from pinkish-red to almost ashen grey. At this point many of the subjects began to cease sweating. GOLD suggests that the primary event in the circulatory collapse of heat pyrexia is high-output cardiac failure, and that the cessation of sweating results from the rising venous pressure.

A pronounced increase in the circulation through the skin and a rise in cardiac output are normal responses to extreme heat. In this sense these features, and presumably also a rise in forearm venous pressure, will precede heatstroke. But, although his subjects were exposed to sufficiently high temperatures, it does not necessarily follow that GOLD succeeded in his attempt to observe the pre-heatstroke state: in the absence of hyperpyrexia the features of light-headedness and ashen-grey face which he describes are akin to the simple heat collapse or syncope first recorded by DREOSTI,[2] which is a much more common heat syndrome than heatstroke. In heatstroke the face is typically red, and sometimes congested and cyanosed as if the patient had been strangled; and less commonly it is grey through circulatory collapse, which is usually regarded as a late and prognostically ominous result of hyperpyrexia. FERRIS et al.[3] sought, but failed to find, evidence of cardiac failure in 36 patients with heatstroke who had no history of poor cardiac function, and observed peripheral circulatory failure or shock in only 7 of 34 patients. In 7 patients with rectal temperatures above 41·7°C (107°F) they found normal pressures in the femoral vein. AUSTIN and BERRY [4] observed that in 27 of 100 cases of heatstroke the systolic blood-pressure was below 100 mm. Hg, but in these cases the state was distinguishable from the usual picture of peripheral circulatory collapse in that the patients had a hot, dry skin and bounding pulse. It seems likely that when circulatory collapse does develop in a patient with

14. Steck, H. *Ann. Méd.-Psychol.* 1954, **2**, 737.
15. Deniker, P. *Compr. Psychiat.* 1960, **1**, 92.
16. Delay, J. *in* Neuropharmacology (edited by P. B. Bradley, P. Deniker, C. Radouco-Thomas). Amsterdam, 1959.
17. Kalinowsky, L. B. *Amer. J. Psychiat.* 1958, **115**, 294.
18. Brodie, B. B., Shore, P. A. *Ann. N.Y. Acad. Sci.* 1957, **66**, 631.
19. Himwich, H. E. *Amer. J. Psychiat.* 1959, **115**, 756.

1. Gold, J. *J. Amer. med. Ass.* 1960, **173**, 1175.
2. Dreosti, A. O. *S. Afr. J. med. Sci.* 1937, **2**, 29.
3. Ferris, E. B., Blankenhorn, M. A., Robinson, H. W., Cullen, G. E. *J. clin. Invest.* 1938, **17**, 249.
4. Austin, M. G., Berry, J. W. *J. Amer. med. Ass.* 1956, **161**, 1525.

heatstroke, it is preceded, as GOLD suggests, by high-output cardiac failure; but on clinical grounds it must be regarded as a complication and not as an early feature of heatstroke.

In reporting that his subjects began to cease sweating when they were near to collapse, GOLD makes an unsupported prediction. A measurable decline in sweating after an hour or two in severe heat has been recorded by others. For want of a specific term, this feature has been called sweat-gland fatigue, and so far no wholly satisfactory explanation has been found. LEITHEAD and PALLISTER [5] have found that sweating is progressively reduced by depletion of body water, and BANNISTER [6] has reported that after intravenous injection of bacterial pyrogens sweating ceases temporarily. Apparently both dehydration and infection may predispose to heatstroke, although neither is a necessary prelude. Whether sweat-gland fatigue, which is known to be independent of dehydration, plays an important part in the onset of heatstroke is undecided. A person who seems to have stopped sweating—who, in other words, has a completely dry skin when those around him sweat profusely—is not necessarily on the verge of heatstroke. SARGENT and JOHNSON [7] observed a man first on a day in which he developed abnormally dry skin and weakness and giddiness while marching in a hot climate, and secondly on the following day when, still with a dry skin, he resumed marching. He marched at 3·75 m.p.h. for 1·5 miles with a peak rectal temperature of 38·5° (101·4°F) and an evaporative fluid loss of 850 ml. per hour—which implies that sweating occurred.

In support of his suggestion that a rise in venous pressure may account for the cessation of sweating so characteristic of heatstroke, GOLD draws an analogy with the observation by BURCH [8] that thermal sweating is diminished in congestive cardiac failure. Such an analogy is justified only if, in terms of increased venous pressure, exposure to severe heat has much the same effect as congestive cardiac failure coupled with exposure to the moderate heat—40°C (104°F)—employed by BURCH. And if this assumption is correct, there remains the question of why a rise in venous pressure should cause a reduction in sweating. The decline in sweating in congestive cardiac failure may be an expression of the associated sodium and water retention and hyperaldosteronism; a similar mechanism has been suggested for the reduction in sweating which accompanies dehydration.[5]

A clear understanding of the onset of heatstroke will surely come, but to expect the incidence to be reduced thereby would be unrealistic. Proper application of what is already known of the principles of prevention would make heatstroke in controlled communities, such as Servicemen, less common than it is; and, in areas where heatstroke is known to occur, devices for effective cooling, such as that described by GUTHRIE and MCCRACKEN,[9] should be at hand.

5. Leithead, C. S., Pallister, M. A. *Lancet*, July 16, 1960, p. 114.
6. Bannister, R. G. *ibid.* p. 118.
7. Sargent, F., Johnson, R. E. *ibid.* 1960, i, 1018.
8. Burch, G. E. *Amer. J. med. Sci.* 1946, **211**, 181.
9. Guthrie, J., McCracken, A. V. *Lancet*, 1960, i, 682.

Community Mental Care?

APPREHENSION, as well as hope, accompanies those developments in psychiatry which have latterly been called "community mental health". The doubts represent not merely an awareness of practical difficulties but also much deeper feelings which have always coloured the attitude of society towards mental illness. The term "alienist" indicated the function allotted to psychiatry—to remove out of sight, into a locked security, those whose departure from normal patterns constituted a problem outside. This problem is not only one of disturbed behaviour: it also includes the anxiety aroused in any society by the deviant and by unrestrained emotions in the mentally ill. Thus it was that the service which took care of the insane became almost completely isolated from the main currents of medicine—both preventive and therapeutic. General hospitals, family doctors, and the public-health services had no more part to play in this custodial care than the mental hospitals generally had in the problems of emotional conflict; and the first big break in this isolation did not come till the introduction of the National Health Service. The tripartite character of the new regime made progress slow, and so did antiquated legal forms; but about the same time effective treatment became a reality for much of psychiatric illness, and its benefit was seen both directly and in the extra confidence given to psychiatric staff. At the same time again, and largely through these changes, the public's attitude of fear and suspicion began to alter.

Today, in a period marked by the introduction of the Mental Health Act, the overwhelming need is for integration of the different services involved; and this theme was embodied in a quadripartite conference held last week by four bodies which have equally important parts to play in the progress of mental health—the Central Council for Health Education, the College of General Practitioners, the Royal Medico-Psychological Association, and the Society of Medical Officers of Health.

Education in mental health was a major subject; and, though education of the public was mainly discussed, dissatisfaction with the place of psychiatry in medical training was generally expressed. Even if psychiatry is adequately taught as a subject, its approach is generally ignored in the other departments of teaching hospitals; and this deficiency is felt alike by family doctors and by those in public health who want to do their part in a comprehensive mental health service. Discussing public attitudes, Dr. I. G. GORDON-SMITH pointed out that community care may be impossible if the fears and fantasies of significant relatives are ignored; and, in dealing with the attitudes of those relatives who are decisive in the patient's environment, social workers can sometimes change the situation. As for the patient, his attitude towards a psychiatric illness presents an illuminating contrast with that towards a socially approved illness, such as appendicitis. An acute feeling of guilt is likely to be present, based on the conviction that the illness would have been avoided if he had

exercised more effort or responsibility; and the belief that it is hereditary may result in his waiting anxiously for it to appear in all the other members of the family. Explanation that such emotions as hate, fear, and guilt are part of the normal mind may come as a revelation, but are quite likely to arouse resentment or rejection. Another speaker said that viewers' letters, following the B.B.C. television series "The Hurt Mind," showed that the public stereotype of mental illness includes violence as its main feature. This feeling of people around him that he may erupt into an aggressive outburst at any moment must clearly be a matter of concern to the psychiatric patient. Methods of mental-health education, described by Dr. A. J. DALZELL-WARD, lay stress on social skills, such as parentcraft and the fostering of good personal relationships, aiming to make use of personality assets. As with other preventive measures, their direct effects are almost impossible to measure, but there can be no doubt of the need they try to satisfy.

Attitudes were also mentioned in the account of rehabilitation and resettlement, by Dr. J. K. WING. The functional disability caused by disease may do less harm than the patient's own attitude towards it, or the social handicaps imposed by other people. In mental hospitals, increase in the length of stay seems to be related to a steady lessening both of the desire for discharge and of the contacts maintained by relatives. It is estimated that nearly half of long-stay schizophrenics (who form 70% of the whole long-stay population) have given up all thought of returning to the community. Yet many such patients who have stable behaviour and only moderate symptoms are capable of a useful day's work—given the necessary change of attitude. It is noteworthy that the acute case coming into a mental hospital enters a culture profoundly influenced by the character of its long-stay wards: there cannot be a full community service unless admission for psychiatric treatment is readily accepted by the public, and this will not occur until the long-stay wards are therapeutic rather than custodial. But community care can be truly preventive, by discovering and treating psychiatric illness at an early stage, before the tolerance of relatives has been strained to its limit; and this may be an answer to some of the fears expressed.

Dr. WING said that current follow-up studies by the Medical Research Council of discharged schizophrenics in London showed that aftercare arrangements are very far from complete. Many do not keep follow-up appointments or bother to take further medication. It is clear that the main burden of their care is falling on the family doctor, and this was emphasised also by Dr. S. I. ABRAHAMS. The family doctor is the one who bears a continuing responsibility for the patient and who must coordinate the services applied. If he cannot do so, the patient may receive piecemeal or even conflicting attention, which ignores him as a person. Nobody, however, has the responsibility of making the family doctor aware of the many services—Government, local-authority, and voluntary—which may help him. Dr. ABRAHAMS described how he began to meet regularly the health visitors who worked in the area of his practice, and how he discovered that their activities had been almost completely unknown to him before. That available services should be fitted to the needs of the individual patient was stressed by Dr. I. G. DAVIES, of the Ministry of Health. In community care, it is necessary to apply the whole range of legislation comprehensively, rather than try to put the patient in a single compartment. Expert clinical and social guidance is needed to deploy these services so that help can be given most effectively, and there should be a well-defined chain of clinical command. The quality of services provided, Dr. DAVIES said, would greatly influence the tolerance of the community and thus the success of community care.

Over and over again this conference returned to attitudes and their importance. Attitudes of the public to mental illness in themselves and others; of psychiatrists to their patients, both acute and long-stay; of doctors and health workers to their colleagues in other services (many of whom may now be unknown to them); and of families to those public services which aim to help them. Education and cooperation were the measures called for to deal with long-established patterns of rejection and isolation.

Renal Papillary Necrosis

RENAL papillary necrosis is an ischæmic infarction of the medullary pyramids, often confined to the papillæ, sometimes involving the more central part of the pyramid, but never extending to the cortex or to the interpyramidal medulla; thus the term "papillary necrosis" probably indicates the site of the lesion better than "medullary necrosis". Because the condition is often accompanied by infection it was commonly called necrotising papillitis, but inflammation is not always present. Two articles have brought together much of the widely scattered information about this disorder. In the first of these, LAULER et al.[1] describe 5 cases, and analyse the clinical features of 250 histologically proved cases (mostly acute fulminating or at least subacute); while in the second LINDVALL [2] reports in detail the X-ray appearances of 155 more chronic cases examined during life.

In 1877 FRIEDREICH [3] first described necrosis of the renal papillæ in a man with enlarged prostate and hydronephrosis, and a few years later TURNER [4] reported instances in patients with tuberculosis, rheumatic carditis, and diabetes, establishing its association with back-pressure on the renal pelvis and sepsis and its occurrence in each sex and in both diabetic and non-diabetic patients. For the next fifty years little further was heard of the condition, and then from various countries came reports of series of cases mostly emphasising its close association with diabetes—especially when complicated by acute pyelonephritis, though it was

1. Lauler, D. P., Schreiner, G. E., David, A. *Amer. J. Med.* 1960, **29**, 132.
2. Lindvall, N. *Acta radiol., Stockh.* 1960, suppl. 192.
3. von Friedreich, N. *Virchows Arch.* 1877, **69**, 308.
4. Turner, F. C. *Trans. path. Soc. Lond.* 1884–85, **36**, 268 *ibid.* 1885–86, **37**, 290; *ibid.* 1887–88, **39**, 159.

suggested that the necrosis was a form of diabetic gangrene.[5] This period coincided with the prolongation of life of diabetics. LINDVALL [2] shows that such cases are now less common; but they will continue to arise because some diabetics will always default, especially in notifying complications. In most non-diabetics with papillary necrosis, increased intrapelvic pressure and secondary infection were found. DAVSON and LANGLEY [6] pointed out that, if increased pressure on the blood-vessels of the pyramids was the sole cause of the necrosis, it was surprising that this was not commoner in hydronephrosis; but later evidence of the healing of necrosed tips [7] suggests that the well-known X-ray appearance of flattening of the papillæ in hydronephrosis may represent the end-result of papillary necrosis. While in most such cases the patient is elderly, because of the causal conditions, the disorder is also found in children in association with acute lesions: STIRLING [8] reported 2 instances in acute pyelonephritis, a 3rd in renal-vein thrombosis, and a 4th with small arterial infarcts and thrombosis of venous radicles; and MARKS [9] has lately reported the condition following exsanguination in infancy. Thus infection by itself or poor circulation by itself may cause the necrosis.

In the past eight years there have been reports in Switzerland and Scandinavia [10] of a great increase in the number of cases of papillary necrosis following excessive use of phenacetin compounds. In LINDVALL's series of 155 patients examined radiologically for changes indicating renal papillary necrosis, there were relatively few with diabetes or chronic urinary obstruction, and the majority had taken phenacetin in such quantities as possibly to lead to damage: in all the kidneys examined histologically, either after resection or post mortem, the changes of chronic pyelonephritis, often with acute exacerbation, were found just as in the diabetic and obstructive cases. The phenacetin may have been taken owing to the obscure symptoms of the pyelonephritis, though LINDVALL admits that phenacetin may render the kidney more susceptible to infection. It is perhaps fortunate that in this country aspirin, and not phenacetin, is the main constituent of headache powders.

Other factors suggested as causal, such as drugs,[11–13] toxins (coliform or staphylococcal), or disordered fat metabolism, have been less clearly substantiated. Some of these act on the vascular supply. BAKER's [14] work on the blood-supply of the renal papilla shows how vulnerable this is to diabetic arterial disease, infection, and back-pressure on the calyces. One source of supply is the vasa recta coming down from the juxtamedullary glomeruli; in diabetes or chronic pyelonephritis many of these may be fibrosed, while in infection the vessels are liable to septic stasis. The other source is branches from the plexus of spiral vessels in the calyx, these branches running over the fornix of the lesser calyx and back superficially to the apex, thus being liable to periarteritis and endarteritis in infection and to obstruction in back-pressure.

Papillary necrosis manifests itself in no special clinical syndrome, the symptoms and signs being those of the associated and causal disease. But suspicion may be aroused by colic due to ureteral passage of the necrotic material, and the surest diagnostic sign is the finding of such material in the urinary sediment. The possibility of diagnosis by renal biopsy [1] should perhaps be regarded with reserve. In the more chronic cases, where urography is not liable to increase back-pressure on the pelvis, LINDVALL [2] has shown that, with highly selective contrast medium, intravenous pyelography can reveal definite "ring" changes in the renal papillæ, formation of cavities in the pyramids or at the papillæ, and the outline of concretions formed round necrotic fragments.

5. Edmondson, H. A., Martin, H. E., Evans, N. *Arch. intern. Med.* 1947, **79**, 148.
6. Davson, J., Langley, F. A. *J. Path. Bact.* 1944, **56**, 327.
7. Schourup, K. *Acta path. microbiol. Scand.* 1958, **44**, 168.
8. Stirling, G. A. *J. clin. Path.* 1958, **11**, 296.
9. Marks, I. M. *Lancet*, Sept. 24, 1960, p. 680.
10. See *Lancet*, 1959, i, 84.
11. Levaditi, C. *Arch. int. Pharmacodyn.* 1901, **8**, 45. Mandel, E. E., Popper, H. *Arch. Path.* 1951, **52**, 1.
12. Rehns, J. *Arch. int. Pharmacodyn.* 1901, **8**, 199.
13. Oka, A. *Virchows Arch.* 1913, **214**, 149.
14. Baker, S. B. deC. *Brit. J. Urol.* 1959, **31**, 53.

Annotations

THE LEADERS AND THE LED

SINCE scientific research became a popular and even reputable way of earning a living, its motives, organisation, and rewards have been favourite subjects for orations. Most of these are heard, praised, and forgotten. Research continues because some men are incurably curious, some ambitious, and some slaves to conformity: today it is not a hobby pursued in the intervals of teaching but a way of life which (some would say) must be interrupted as seldom as possible by more banal duties. Nevertheless it has its problems, and a lecture given at St. Andrews by Sir Lindor Brown [1] deals with one which is not the less important because it can be solved by no general rule. Sir Lindor's tenure of a chair in a department once graced by Bayliss, Starling, and Hill not only has made him the intellectual father of pupils all over the world but must have provided ample material for thought on the relations between "the chief" and his juniors in the research laboratory.

Analogy is a dangerous tool in argument, but the similarities between scientific research and the creative arts is too striking to be overlooked. In painting and science alike, there are basic methods which are best learnt at the master's feet. The beginner will want advice on the choice of a subject which will be within his powers and which will have a foreseeable end. (The scientific homologues of Haydon's gigantic canvases are seldom published.) The artist and the scientist both know the alternations of hard dull work, of despondency and idleness, and of what must be called—for want of a better word—inspiration. It is general experience, too, in both faculties that the tiro does better if he spends his days among others of like interests. Old men may be solitary by choice and remain productive, but the young learn more by coffee-housing with their fellows. All this throws great responsibility on the professor, and it is with him and his problems that Sir Lindor is concerned.

1. The Perils of Leadership in Science. Sir David Russell Memorial Lecture, University of St. Andrews. By Sir LINDOR BROWN, F.R.S. London: Oxford University Press. 1960. Pp. 20. 3s. 6d.

But, as he says, the same problem arises whenever there is a difference of age and experience between two members of the same department, and it will always be complicated —sometimes beyond solution—by personal whims and antipathies.

In England and the United States professors are often regarded very much as other men. In Scotland their title counts for more, while in middle Europe they have power and fame beyond the dreams of the most ambitious savant here. The advantage, probably, is with the English student. Some things he must temporarily take on trust, but it will be better for him if these are derived from sources wider than the infallible wisdom of one great man. (The pains of disillusion can be very real.) Even in England there is wide diversity in the relations between the professor and his pupils. He may welcome them kindly; suggest—very diffidently—a programme of work; and then disappear for six months into a maze of committees, congresses, and delegations. He may on the other hand direct their labours so diligently and minutely that they are led to regard themselves as so much cheap labour. It is said that in one university department no research assistant is allowed to discuss his work with any colleague: all the strings lead back to one pair of hands, the professor's. Sir Lindor suggests—and experience supports him—that the best teacher is one who still finds time to work at the bench with his own hands. It is a comfort to the beginner to see that the experiments of a revered elder may end in abysmal failure on occasion. A daily comment may save hours of useless toil. Above all, the beginner will learn that research is something more exciting than mere work: it can, in fact, be fun.

Buonaparte said that no man can give orders to more than six subordinates, and on the whole a small department is a better place for learning than a large one. No man—not even the most distinguished Herr Geheimrat Professor—can advise expertly on every branch of a subject such as physiology, and it is better that the pupils be assigned to the care of those who are engaged in active research in their province. But the professor's responsibilities do not end there. He has seen more, read more, and thought more than anyone else in the department, and the pupils may find that even infrequent visits from Olympus will bring flashes of enlightenment. One may add that the outstanding teachers seem to share one quality which is seldom made public until their obituary notices are written: they earn the personal devotion of their pupils to the point of idolatry. Outsiders can sometimes get a hint of this from their nicknames.

POLIOMYELITIS AND THE BRAINSTEM

THREE physiological mechanisms in the brainstem may be involved by poliomyelitis—the lower motor neurones, the respiratory " centre ", and the circulatory " centre ". The motor nuclei in the brainstem are analogous to the anterior horn cells of the spinal cord, and it is therefore not surprising that they may be affected. One result of involvement of these nuclei is paralysis of swallowing; and, if care is not taken to protect the airway, the patient may die. If he survives, the power of swallowing almost always recovers. Involvement of the respiratory and circulatory " centres " is less easily evaluated. This is partly because these " centres " are not sharply localised regions like the cranial nerve nuclei, and, despite recent progress,[1] their various parts are not yet clearly mapped anatomically or understood physiologically. They constitute, however, part of the reticular formation of the brainstem, and there is ample evidence that poliomyelitis can damage this.

It has long been supposed that respiratory failure in poliomyelitis may be due to involvement of the respiratory centre, and irregularity of respiration is usually regarded as one of the principal diagnostic features. Bower,[2] however, with an enormous experience of poliomyelitis in California, states that in most cases with so-called respiratory-centre involvement this centre is not involved at all. The more carefully the patient is examined, his airway kept clear, his breathing assisted, and his electrolytes maintained at normal levels, the less commonly is involvement of the respiratory centre invoked to explain the clinical signs. In the great majority of cases respiratory failure in poliomyelitis is due to paralysis of the respiratory muscles—that is, to involvement of the thoracic part of the spinal cord and the fourth segment of the cervical cord from which the phrenic nerve arises.

Patients with poliomyelitis are subject to circulatory disturbances. Spencer et al.[3] indicate that such disturbances arise in about a third of patients with acute life-threatening poliomyelitis; but the ætiology is very varied and in acute cases it is usually difficult to distinguish the parts played by hypoxia, hypercapnia, alterations in tissue electrolytes and pH, myocarditis, lesions of the circulatory centre, and the effects of artificial respiration. When the acute phase of the disease is over, many of these factors cease to be important; but, as has been known for years, patients who have had poliomyelitis are liable to hypertension.[4] Zimanyi et al.[5] in Hungary have studied 336 bedridden patients in whom poliomyelitis had developed at least twelve months previously. 26% had hypertension. The incidence was highest in those who were most extensively paralysed, in those who had required artificial respiration, and in those with encephalo-bulbo-spinal, as opposed to purely spinal, disease. Zimanyi et al. argue that the hypertension is due to an alteration in the central nervous mechanisms controlling the blood-pressure—in short, to involvement of the circulatory " centre ". They also emphasise, however, that extensive wasting of muscle entails a decrease in the vascular bed, and therefore an increase in total vascular resistance. In health a rise in blood-pressure following increased total vascular resistance is prevented by reflex reduction in cardiac output, which restores the blood-pressure to normal. When the healthy subject is at rest, vascular resistance to blood-flow through the muscles is great and yet the blood-pressure is not raised, and it is improbable that in poliomyelitis the total vascular resistance is so much increased that reflex responses cannot compensate for this increase. Another explanation for persistent hypertension in poliomyelitis is renal infection. In severe cases of poliomyelitis catheterisation of the bladder is usually required, and urinary infection is common. In the Hungarian study, however, patients with suspected urinary infection were excluded. Riley and Knight[6] showed that of 60 patients with severe paralysis due to poliomyelitis, 44 had urinary infection and 10 had persistent diastolic hypertension. They were, however, reluctant to associate these two

1. *Physiol. Rev.* 1960, **40**, supplement 4, pt. 2.

2. Bower, A. G. Diagnosis and Treatment of the Acute Phase of Poliomyelitis and its Complications. London, 1954.
3. Spencer, A. W., Jackson, R. R., Vallbons, C., Harrison, G. M. *Amer. Heart J.* 1960, **59**, 384.
4. Weinstein, L. *Circulation.* 1957, **15**, 735.
5. Zimanyi, I., Prohaszka, M., Szondy, M., Ormai, S. *Acta. med. scand.* 1959, **164**, 497. See *Lancet*, 1959, ii, 120.
6. Riley, H. D., Knight, V. *Medicine, Baltimore*, 1958, **37**, 281.

complications closely; for they could not correlate the severity of urinary infection with the appearance of hypertension, and in cases where the time of onset of hypertension was known it was earlier in the course of the disease than would be expected if it had resulted from renal infection.

It seems that poliomyelitis can indeed affect the circulatory and respiratory "centres"; but it is probably unwise to diagnose such involvement except with great circumspection.

A FRESH START FOR THE SCHOOL DENTAL SERVICE?

THE deplorable state of the school dental service was mentioned by Mr. Duncan MacGregor [1] in his presidential address to the British Dental Association, when he declared that the dental welfare of children was a "national scandal". The situation is becoming worse, and nothing effective is being done to make it better. Perhaps action will be expedited by a report [2] in which the British Dental Association describes the service's rise and present decline.

The first school dental clinic was opened in Cambridge in 1907, but not until the passing of the Education Act, 1918, were local authorities obliged to provide dental treatment for schoolchildren. In 1936 the Board of Education recommended that there should be 1 dentist for every 5000 children in urban areas, and 1 for 4000 in the country. More recently, the Minister of Education has suggested that, for a complete dental service, 1 dentist for every 3000 children is needed. Actually, since 1938, when in England and Wales there was 1 dentist for 5300, there has been a steady fall in numbers, except in 1947, when the ratio was 1/5000. 1957 was the worst year (1/8000), and since then the position has improved slightly (1/6800 in 1958). But there is no sign of any sustained increase, and the ideal ratio of 1/3000 seems completely unattainable. As for dental treatment for nursing and expectant mothers, and preschool children, the British Dental Association says that "the title 'priority dental services' has no meaning at all in practice". In fifteen years, it is estimated, 45% of the present full-time dental officers will have retired, and the chances of filling their places seem remote.

Apart from the general shortage of dentists, it is quite plain that not enough of them want to make school dentistry a permanent career. For this, the British Dental Association says, there are four main reasons: (1) the attitude of the local authorities to the dental services, (2) their attitude to the professional staff, (3) the poor prospects of a career in local-authority service, and (4) the low and unrealistic salaries offered. The view taken by most local authorities that dental surgeons are primarily local-government officers, and only secondarily dentists, must deter many young practitioners. The British Dental Association suggests that senior dental officers should be in full control of the dental services in their areas, and should no longer be subjected to the control either of doctors or of local-government officers. More senior posts are needed; and salaries comparable to incomes in private practice, and with increments which do not cease after eight years' service, must be offered if the school dental service is to be saved from certain collapse.

An independent report by Mr. H. R. Cullwick,[3] a Staffordshire dental surgeon, calls for the establishment of an autonomous school dental service, directly responsible to the Minister of Health. He proposes—and his proposals are endorsed by some leading members of the dental profession—that the new service should treat children from 3 until school-leaving age. Salaries for dental officers would start at £2000, increasing to £2300; senior dental surgeons would receive up to £5000. Money could be saved, Mr. Cullwick suggests, by supplying all clinics from a central depot. For at least ten years the new service would cost more than the present one, and to offset this he proposes that adult patients, with certain exceptions, should pay the full cost of dentures.

DIAGNOSIS OF MEDIASTINAL MASSES

IN the diagnosis of lesions of the mediastinum the first and most important step is to determine exactly where the lesion lies, since the type of lesion to be expected varies with the site in the mediastinum: the predilection of neurogenic tumours for the upper two-thirds of the posterior mediastinum is well known.[4] Plain films, tomography, and screening are all useful in determining the site; and careful screening may yield further information, such as the presence or absence of pulsation and (with pleuropericardial cysts, for instance) the change in shape during respiration and Valsalva's manœuvre. In addition the presence or absence of calcification can be determined, and the relation to the main pulmonary arteries may provide information as to whether some opacities are glandular. Most mediastinal lesions either displace other mediastinal structures into the lung field or carry the pleura in front of them, and nearly all present as a smoothly outlined opacity; it is only in the later cases of malignant neoplasms or in the presence of infection that this smooth outline is lost. Again, evidence of rate of growth may indicate malignancy or infection; and, in lesions which are situated posteriorly, examination of the dorsal spine for bony destruction, infection, or enlargement of the foramina may prove of diagnostic value. But commonly with lesions involving the upper middle and anterior mediastinum the inner border of the lesion cannot be demonstrated, and the outline of the lesion cannot be distinguished from the shadows of the great vessels by tomography, straight films, or screening. Anomalously, aortic aneurysms are often still, whereas neighbouring cysts often appear pulsatile and sometimes apparently expansile.

To differentiate between these lesions additional information is usually needed. Kincaid et al.[5] have examined 200 such cases by contrast injection, either by angiocardiography or by direct thoracic aortography. The patients had previously been investigated by other methods. In half the cases the findings by fluoroscopy were indeterminate, and in a quarter frankly misleading. Tomography and bronchoscopy similarly were of no definite diagnostic value, whereas contrast injection always revealed vascular lesions, such as aortic aneurysms, and confirmed that anterior mediastinal tumours were not aortic in origin. In addition contrast examination proved helpful in planning the operative procedure, either by showing malignant invasion of the large vessels—particularly the superior vena cava—or by indicating the length

1. See *Lancet*, Aug. 13, 1960, p. 358.
2. Memorandum on the Local Authority Dental Services. *Brit. dent. J.* 1960, **109**, 275. Reprints obtainable from the British Dental Association, 13, Hill Street, London, W.1.
3. See *Birmingham Post*, Oct. 4, 1960.
4. Curreri, A. R., Gale, J. W. *Arch. Surg., Chicago*, 1949, **58**, 797.
5. Kincaid, O. W., Brandenburg, R. O., Bernatz, P. E. *J. Amer. med. Ass.* 1960, **173**, 613.

of graft required when the vessels were involved by non-malignant lesions. Of the 200 cases examined, 188 were subjected to the potentially safer investigation of angiocardiography and only 17 to direct thoracic aortography. Kincaid et al. recommend the use of either sodium diazotrizoate or methyl glucamine diazotrizoate; and, except for one case in which the medium was accidentally injected into the soft tissues of the antecubital fossa, no serious side-reactions were noted.

GOVERNMENT BY APPOINTMENT

ONE of the social developments of recent years in this country has been the establishment, under State auspices, of public services administered largely by members of the public. Previously government had vested almost entirely in two groups—politicians (national and local) elected by democratic franchise, and professional administrators recruited in accordance with rules designed not only to test their qualifications but also to avoid patronage. The new services, however, have been largely entrusted to boards and committees whose members are neither politicians nor Civil Servants but are hand-picked for their task.

Of this new system the National Health Service is perhaps the most striking illustration. In England and Wales there are 15 regional hospital boards whose chairmen and members are appointed by the Minister of Health, and 382 hospital management committees appointed by the regional hospital boards; the boards of governors of the 36 teaching hospitals are also appointed by the Minister of Health. In Scotland there is a similar pattern; the Secretary of State appoints 5 regional boards, and these in turn appoint 84 boards of management. For the general-practitioner services each county and county borough (except in a few cases where there are amalgamations) has an executive council with subordinate committees, a fifth of the council members being appointed by the Minister. Appeals against the decisions of the executive councils on matters of discipline go either to the Minister or to the National Health Service Tribunal—itself appointed by the Minister though the chairman is chosen by the Lord Chancellor.

A broadsheet from P.E.P.[1] suggests that the administration of public services through boards and committees now involves something like 40,000 posts at national, regional, and local level. The use of appointed boards and committees in preference to the elected local authorities has come to stay—first, it is suggested, because of the need to secure people with particular qualities for particular jobs, and secondly because of the Minister's need to exercise some form of remote control.

In considering the new arrangements, we should note that, though some boards comprise highly paid full-time members, most of the appointments in question are part-time and unpaid: thus the boards and committees which do so much to administer the health services are almost entirely composed of part-time voluntary members. Again, the appointment of some boards and committees may be preceded by a good deal of consultation. As the P.E.P. broadsheet points out, the Minister of Health, before appointing members to the regional hospital boards, consults universities, representative medical organisations, local health authorities, and other bodies such as hospital associations and trade unions; sometimes the chairman of the board is also consulted. In appointing hospital management committees, the boards again consult various interested organisations—e.g., trades councils, the Royal College of Nursing, hospital contributory schemes, women's institutes, the Red Cross, the St. John Ambulance Brigade, the Women's Voluntary Service, and chambers of commerce. Such consultation is of great value in providing names of possible candidates, and it also stimulates the interest of the bodies consulted. But the Minister and the hospital boards are not limited to names put forward in this way, and the person appointed serves as an individual and not as the representative of any organisation.

Apparently, however, consultation on this scale is not typical of the other public services. For example, in appointing its tribunals, the National Assistance Board seems to rely almost entirely on the recommendations of its own local officials. Lack of adequate consultation may be responsible for what P.E.P. call "excessive plurality" in public offices, every member of the London County Council holding (it is said) an average of nearly six other public posts. Some plurality is of course desirable, but there is strong evidence that too few people have too many appointments. Possibly the number of people able and willing to undertake voluntary public service is not so great as might be supposed, or perhaps there is an official tendency to "play safe" and to appoint only known and trusted people.

The P.E.P. broadsheet is almost entirely devoted to the problem of how members should be appointed to boards and committees; but the development of the system raises larger questions that will someday have to be considered. Is administration by appointed committees efficient? Are the most suitable persons found? Should the Government have such large powers of appointment? And is it true that Ministers have more control over appointed boards than over local authorities? As regards this last question, we should say that they probably have not; for Whitehall can and does control the activities of local councils in considerable detail. In the health service the advantage to be claimed for "government by appointment" appears to be twofold. First, it enables the service to be administered by mixed committees of laymen and doctors. (We do not ourselves rate this advantage high, since we believe that medical influence can be exerted more effectively through strong advisory committees, as was usual in the voluntary hospitals.) Secondly, the wide consultation undertaken by the Minister and the boards makes for the selection of laymen who may be more representative of the public whom they serve than elected councillors would be.

1. Government by Appointment. *Planning*, 1960, **26**, no. 443. Published by Political and Economic Planning, Queen Anne's Gate. Pp. 19. 3*s*. 6*d*.

The Earl of LIMERICK has been reappointed a member of the Medical Research Council, and Mr. E. F. COLLINGWOOD, SC.D., appointed a member in succession to Sir Geoffrey Vickers. Lord Limerick will serve as chairman and Dr. Collingwood as treasurer. Dr. THEODORE CRAWFORD, professor of pathology in the University of London at St. George's Hospital Medical School, and Dr. W. M. MILLAR, Crombie-Ross professor of mental health in the University of Aberdeen, have been appointed members in succession to Prof. G. Payling Wright and Dr. Denis Hill, who are retiring.

Prof. J. M. MUNRO KERR, emeritus regius professor of midwifery in the University of Glasgow, died at Canterbury on Oct. 7, at the age of 91.

Special Articles

PATHOLOGISTS AT THE CROSSROADS*

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AT the present time there is much very sincere, yet sorely troubled thinking about the future organisation of pathologists.

For the title of this address I use the words " at the crossroads " with full realisation that a crossroads is a place from which one can proceed in a variety of directions—onwards to a new destination, to right or to left, or just plain backwards. Before we can reach any valid conclusion about what course to pursue, we must try to understand the causes and the distribution of the present discontent among pathologists.

So far as I can ascertain, the unrest is chiefly on the part of the younger consultants in hospital pathology and those who have not yet reached that rank; but many of the more senior men, and some academic pathologists also, have engaged themselves in the matter actively because they are anxious to do everything in their power to ensure that the pathologist of the future shall be able to enjoy a professional career in the most favourable circumstances.

* * *

In thinking of the pathologist, whether at the crossroads or elsewhere, we must first take into account the nature of his work, and this seems to me to fall into two main classes. Pathology has been defined very generally as the study of disease by scientific methods, and it has two main purposes—namely (1) to advance fundamental knowledge of the nature of disease and of the mechanisms by which disease is produced, and (2) to apply existing knowledge to the diagnosis and prevention of disease with a view to facilitating treatment, even if the latter is not properly the concern of the pathologist in other than an advisory capacity. It may be that one of the causes of present discontent lies in the drift apart of these two functions, as Dible has stated, and we should inquire into the practice of clinical pathology in this country to see whether we can improve it and remove the causes of the disquiet.

The continued advance in technical methods has multiplied very greatly the demands upon the laboratory for routine tests, and there are few laboratories, if any, where the technical staff has grown in proportion. Several of our most distinguished colleagues have expressed anxiety on this score and deprecated the almost total submergence of the clinical pathologist in carrying out routine tests at the behest of the clinician—a position which may well induce a feeling of inferiority if the pathologist has no say or choice in the selection of the work he has to do, and allows himself to be used as one whose work is merely ancillary to that of the clinician. There is no single remedy for this overloading of existing resources; but as far as possible merely technical work should be allotted to technicians, so that the pathologist shall have more time to widen and advance his fundamental knowledge as an exponent of one of the basic sciences of medicine on which clinical work is founded.

The medical and technical staff of hospital departments has all too often been kept at so low a level that energies are wholly spent in getting through the day's work, and this is all the more true when the duties involve so-called emergency calls at night and at weekends, not all of which are real emergencies. The clinical pathologist could be protected by the senior clinician from exploitation of this kind; but such discrimination and care are less likely to be exercised on his behalf if the pathologist allows himself to be relegated to the position of a mere servant of the wards.

The volume of hospital work has increased by virtue of a law that antedates Parkinson—namely, that the successful research of today becomes the routine of tomorrow. It is not so long ago that the pathology department of the hospital was known as the research department, and it is part of our duty to see that the title shall continue to be worthily applied.

* * *

It is to the credit of pathology that it brought medicine freedom from the shackles of Galenic authoritarianism; and it is still true that research in the laboratory in one or other of the four branches of pathology is the chief source of the increase in scientific clinical knowledge that is so striking a feature of medicine today.

The first of its four constituent disciplines to develop was morbid anatomy; and the morbid anatomist and histologist was trained largely on the apprenticeship system, rather unsystematically, but with lots of room for individuality. Of all the divisions of hospital pathology, the diagnostic problems in morbid anatomy and histology are the most exacting and the most personal. There are no controls, there are no tables of biological reactions such as can be applied to bacteria, and there are no standard solutions such as the chemist uses to check his results and set his confidence limits. There is only the pathologist, the sections, and the microscope, and his experience to guide him.

Bacteriology was the second of our disciplines to evolve; and, although much of the routine hospital work can be carried to the reporting stage by the trained technicians, hospital bacteriology offers a rewarding field to the trained and inquiring mind in the tracing of outbreaks of infection and eradicating the causes, in ensuring sterility, in controlling cross-infections, and in understanding how and why bacteria come to cause disease, and how it can be cured or averted. In addition, more academic biological bacteriology is also open to those whose interests lie in that direction. I shall no more than mention virology—a younger relation of bacteriology but one rapidly going its own way. The interactions of bacteria and viruses present fundamental questions of which we have only begun to glimpse the answers.

Hæmatology is the discipline that has retained the closest connection with clinical medicine; and indeed it is still practised by physicians to such an extent that this division of clinical pathology sometimes operates more under the department of medicine than of pathology. Here too the rapidly advancing technology of the subject is tending to lead to greater specialisation, and I believe that general physicians are gradually handing over more and more of the routine investigation of all hæmatological problems to that division of clinical pathology. In view of the ever-increasing complexity of the blood-groups and of cross-matching techniques, of the progressive subdivision of the clotting factors into more and more fractions of clinical significance, and of the elaboration of techniques for the investigation of hæmolytic anæmias and of types of hæmoglobin, it is not surprising that the physician turns more and more to the professional laboratory worker. A certain amount of robot working by electronic

* From the presidential address to the Association of Clinical Pathologists on Sept. 30, 1960.

machines has already been introduced and no doubt more is to come, but there is a large and expanding area in which expert knowledge is required and for which specialised training must be provided within the laboratory.

Our fourth subdivision, chemical pathology, presents special problems. In it, as in bacteriology, a large part of the routine hospital work can be and is increasingly carried out by technicians and other workers not medically qualified. In this field we have recently seen the first serious attempt to introduce automation, and it seems likely that robot analysis will become more popular in hospital departments where large numbers of simple repetitive tests have to be carried out for the control of clinical treatment. Much of the routine chemical pathology of hospital departments can therefore be carried out by workers who are capable of following given directions and are able to assess the accuracy of their results by the use of standardised solutions as controls. Like all simple repetitive work this is unlikely to hold the interest of a lively mind for long; but before the medical graduate can go further in chemical pathology he requires a greater basic knowledge of chemistry and of biochemistry. Without a science degree, he needs further fundamental training, which it is almost impossible for him to receive while engaged in full-time hospital work. The Association of Clinical Pathologists was able to persuade the Ministry of Health that aspirants to chemical pathology might be seconded at the registrar stage for a year of fundamental study in chemistry while receiving full pay. It is hoped that this will enable the supply of would-be chemical pathologists to be increased, but it is as yet too early to know whether the scheme will succeed.

* * *

We can lay down, therefore, a general pattern of development for the young pathologist in training—that he should be given the opportunity to acquire a certain foundation of experience in each of our four disciplines and thereafter take up whichever branch of work his inclinations and opportunities favour. If during this time he can be given a problem to pursue, so much the better. Every effort should be made to encourage this activity. I am convinced that the hospital pathologist will be a better man and will do a better job in his daily routine if he succeeds in combining some research interest with his daily work as soon as he has mastered the initial rotational training. I do not advocate that he should write for the sake of writing, but much valuable observational research remains to be done.

What of the other side of pathology, the so-called academic side? Here teaching and research are the predominant interests and it is the duty of universities to foster them. Where university and hospital appointments are combined, the professor, and especially his fairly senior staff, should not be so overburdened with routine hospital duties that their primary purpose is defeated. Nowadays most professors are glad of a share of the routine as a happy relief from committee meetings and administration, but the lecturer staff can suffer badly unless they are protected by their terms of service.

* * *

We have glanced briefly at the training that the young pathologist is likely to undergo nowadays. At the end of it what has he got to show that he has successfully completed the round and had further experience in one or more fields? If he has stayed in an academic department and been fortunate in his research he will probably have an M.D. or other higher degree by presentation of a thesis on a selected topic. But what of the man who has not been in a teaching department but has been busily engaged in hospital pathology for five years or more under a good group of consultants who have taken the trouble to supervise his training and experience? It appears that he feels a sense of frustration, and sees himself at a disadvantage as compared with his contemporaries in medicine and surgery, because they, after a comparable period of training are likely to have acquired the M.R.C.P. or F.R.C.S. This feeling is likely to be intensified when he has attended a few appointment committees and had to explain why he has no higher qualification. This sense of frustration is one of the most potent causes of unrest today.

In what ways are pathologists made to feel that their position is regarded as inferior? Regarded by whom? Not by themselves, unless they have a guilt complex and feel that they occupy a position of equality that is undeserved. Nor by the administrative authorities; for they have admitted equality in the only way they can, by awarding full consultant status and equal pay. Nevertheless there is a substratum of truth to be uncovered.

In the pre-N.H.S. days there was a widespread custom in England, if not in Scotland, of regarding as ineligible for appointment to the medical staff committee of the hospital anyone in receipt of a salary, even part-time. The non-academic pathologist, to survive at all, was necessarily in receipt of a salary because, in contrast with physicians and surgeons, he had only a very restricted scope for earning a living by private practice. In many cases this meant that the pathologist was excluded from participation in hospital affairs on equal terms with his clinical colleagues because he was thought to have a vested interest. This unwarranted prejudice has, I believe, left its mark on staff relationships to this day. The pathologist's salary was usually part-time and his income had to be supplemented by private practice in clinical pathology, for which he was again dependent on his clinical colleagues.

This continual carrying out of tests at another's bidding, and providing results to establish a clinical diagnosis for which the pathologist may receive little acknowledgment or credit, may have depressed some clinical pathologist's assessment of their own position. I think this is false and unworthy, for if the clinical pathologist so hankers after ultimate responsibility for the care of the patient that he is unhappy without it, he is in the wrong section of the profession. Having chosen his field of work he cannot reasonably grumble if it does not cover those parts of medical practice in which he finds his deepest interest. If prejudice of that kind still survives, surely it must be dying out. Physicians and surgeons, too, are now paid for their hospital services, either full time or part time, and their position is in no way different from our own.

The other chief cause of dissatisfaction however is, worthy of more detailed inspection—namely, the lack of a specific higher qualification in pathology to testify to a general level of professional competence in the chosen subject.

* * *

Higher qualifications in pathology have been under active debate in the Association of Clinical Pathologists since 1947. Many pathologists have expressed the desire for such an examination in the belief that successful completion would give them additional status, if only the examination could be universally recognised as of equal standing with the M.R.C.P. By *status* I understand them to mean that they are thereby acknowledged to belong to a professional organisation or society which is of high

repute, and is therefore presumed to shed some of its lustre on them. It is equally true, however, that the repute of a society depends on that of its constituent members, who by their professional activities determine the place that the society will be accorded by similar professional organisations and within the community.

The comparison most frequently made is with the higher qualifications of the Royal College of Surgeons and the Royal College of Physicians; and so the demand is for something that will not be called merely a diploma, although of course all of them are diplomas. The higher qualifications of these old-established corporations have attained their enviable position at least in part because of the difficulty in acquiring them, as is attested by a pass-rate of 10–15%. Further it is now insisted by the colleges that the possession of these higher qualifications is not to be regarded as anything more than an indication of suitability to undergo further training in clinical medicine or surgery. For this reason many have advocated that the M.R.C.P. should be taken *before* embarking on a career in pathology, for its value as an indication of quality is beyond doubt.

But is the M.R.C.P. the proper examination for a pathologist already in training? This is by no means universally accepted.

The academic affairs committee of the Association was unanimously of the opinion that the M.R.C.P. as it stands could not be regarded as a suitable qualification *in pathology*. This implies no disrespect—the examination is not designed for that purpose. Further, the evidence submitted to us left no doubt that, after a few years of enthusiastic encouragement of their juniors to go for the M.R.C.P., many consultants in pathology had changed their point of view and were now convinced that this examination ought to be taken, if at all, *before* embarking on full-time laboratory training. The reasons for this change of mind are not difficult to find. The high-level clinical examination required of an intending physician is a serious problem for the man who has been working in the laboratory for a few years, for it requires not only the initial education of the senses but the maintenance of skill by constant practice. I have on occasion suggested to clinical examiners that a distinction should be drawn between knowledge of medicine, combined with ability to interpret the history and physical signs, and the technical ability required to elicit and detect the physical signs. This is, after all, the technical skill of the physician, and it is no more justifiable to demand it of the young pathologist than it would be to require the physician taking the M.R.C.P. to perform personally all the laboratory tests thay he quotes so glibly. So long as the M.R.C.P. examination remains in its present form—and there is no prospect of changing it—we must accept that it is not a higher qualification in pathology, however desirable it may be as an indication of general ability and suitability for specialist training. Unless success comes quickly, the effort required to keep up the clinical skill is too great to make it a practical proposition while doing a full day's work in the laboratory. Many heads of departments have had the painful experience of seeing a young man of adequate ability fail to pass at his first or second attempt and thereafter become virtually a passenger in the laboratory until this hurdle had been surmounted.

* * *

After the debate at Exeter in 1953, inquiry by the committee on training of clinical pathologists revealed grave dissatisfaction with the standard of would-be entrants into laboratory work. It was surprising that at a time when promotion in the clinical field was slower and more difficult than ever, there should have been such lack of high-class recruitment into a specialty which was clearly going to expand and was likely to allow promotion to consultant status at an earlier age than in general medicine or surgery.

The shortage of applicants was not universal. I do not think it was experienced by all university departments, and at least we in Scotland had no real difficulty in maintaining the high academic standards to which our departments had been accustomed in pre-N.H.S. days. In this we were, I realise, in a privileged position, very different from that of some non-teaching hospital departments, which were inadequately staffed by technicians, insufficiently supplied with apparatus, and generally at the tail-end of any list of priorities for building or equipment. In thus starving the laboratory service, and almost depriving the pathologists of hope that the rapidly mounting burden of routine work could ever be undertaken in reasonable conditions, the responsible authorities, whether central or local, did pathology a grave disservice and one that is not yet removed. Recent graduates of high ability and promise were discouraged from entry to hospital pathology, and senior consultants in turn were depressed by their failure to attract men and women of the right type.

At this time the cry was again raised that a material factor in influencing high-quality graduates to reject pathology as a career was the absence of a suitable higher qualification comparable to the M.R.C.P. or F.R.C.S. In what ways then, apart from personal pride and satisfaction, does the absence of a higher qualification affect pathologists?

The Health Service Acts have rather elaborate machinery for the filling of all posts of senior-registrar status or higher. In England and Wales representatives of the Royal Colleges sit on all committees for consultant and S.H.M.O. appointments, and in Scotland the procedure, although different in detail, is much the same in practice. Thus it has come about that at committees for the appointment of a pathologist it is not uncommon for candidates who have no higher qualification of any kind to be asked to explain why this is so. Indeed, even when the candidate has the M.D. degree, sometimes it is suggested that this is not an adequate higher qualification because it may have been taken by thesis in a narrow and highly esoteric field of study that affords no guarantee of knowledge and experience in a wide professional field, however much it may indicate intrinsic intellectual ability.

The standard exacted by the universities varies and their degrees are not strictly comparable. Some confer only a pass degree, others award in addition two grades of honours and beyond that, for the highest class, a gold medal. Furthermore, the circumstances under which a thesis is written must influence one's assessment of its merit, for the award of a pass degree to a candidate with all the resources of a university department behind him indicates a less meritorious performance than a similar award to a man working in a peripheral hospital laboratory with fewer facilities at his disposal. Whatever may evolve, I hope that we shall never reach the position that there is only one portal of entry into hospital pathology through which all must pass by virtue of a specific examination. This would, I fear, canalise the entry far too narrowly. The academic departments are relatively few, but the opportunities they offer for scientific training are

of the highest class. Since promotion for all to a professorial chair is impossible, there must be an outlet from academic pathology into hospital pathology, and it is the duty of the heads of academic departments to ensure that the training of their staffs fits them to make the transfer if they so wish.

* * *

As a first approach to a solution of the problems before the Association of Clinical Pathologists, the council in 1953 set up a committee on academic affairs under the chairmanship of Prof. Geoffrey Hadfield to consider the advantages and disadvantages of a College or Faculty of Pathologists, the possible membership and affiliations of such a body if formed, and the practicability of higher qualifying examinations. The deliberations of this body and the views of its members and observers and of the council were presented to the Association in March, 1955, in a masterly report by the then chairman of council, Dr. Cuthbert Dukes, and this report was circulated to all members of the Association. The conclusions then reached by an overwhelming majority were (1) that it was impracticable and inexpedient to attempt to set up an independent college or faculty at that time, (2) that an affiliated faculty under the conditions then prevailing was undesirable, and (3) that the whole question be kept under review. It has, in fact, been under review ever since.

Although there was general agreement to shelve the question of a college or faculty for a period, it was felt that there was need to encourage a more systematic training for new entrants and also to review all the available higher qualifications to determine whether any of them met our needs. A new standing committee on academic affairs which was set up studied the existing examinations and explored also the possibility of an examining board on the lines of the American system. Of the existing examinations the most suitable seemed to be that of the Royal College of Physicians of Edinburgh, in which the candidate professes a special subject selected from a list that includes pathology. But even this examination is not ideal; it includes a normal membership examination in clinical medicine and a good deal of pharmacology and therapeutics. All attempts failed to persuade the Edinburgh college to modify the examination to our requirements by increasing the pathology at the expense of clinical medicine and pharmacology. Thus the Edinburgh M.R.C.P. is actually more difficult for a young pathologist than for a young physician; for the pathologist has to attain the necessary standard both in clinical medicine and in pathology.

As a result of all these deliberations the committee on academic affairs came to the conclusion that none of the existing examinations fully met our requirements and that none of the licensing bodies was prepared to modify an existing examination to our wishes, or to institute a new and acceptable examination for us. For example, conversations with the Royal College of Physicians of London indicated that there was likely to be no great difficulty in instituting a new higher qualification such as a mastership in pathology, but this did not include the offer that successful candidates would thereby qualify for subsequent election to fellowship. Since this appears to be the yardstick by which any examination conducted by the Royal College of Physicians is judged, the proposed mastership was deemed unsatisfactory.

The academic affairs committee then recommended to the council in April, 1958, that official conversations should be begun with the Pathological Society and with the Royal Medical Corporations on the question of postgraduate qualifications in pathology and especially on the nature of the supervising and examining body required for the purpose. This left the door widely open for any approach or discussion. The matter did not long rest there. At the council meeting in June, 1958, resolutions were submitted from three branches requesting that steps be taken forthwith to establish a new body or college to represent pathology. The council, despite the overwhelming body of opinion against such a proposal only three years previously, agreed to set up a "ways and means" committee, under the chairmanship of Prof. G. J. Cunningham to examine and report on how a College of Pathologists might be inaugurated. This committee worked at great speed and reported to the council in October, 1958, on (*a*) the procedures by which a college might be instituted, (*b*) the estimated cost of a college in Central London, and (*c*) the functions that a college ought to subserve.

The committee recommended a referendum to the Association as a whole to determine whether a substantial majority of members now favoured the proposal to set up a college, and, if so, whether they would contribute to it financially. It was also recommended that an approach be made to the Pathological Society to ascertain the views of pathologists other than those practising clinical or hospital pathology. The next step therefore was to prepare and send out to all members a voting paper; but the council laid it down that they could not consider themselves as having a mandate to pursue the matter further unless 75% of the ordinary members voted and of those voting not less than 75% answered all the questions in the affirmative. At the end of the day these requirements were not actually fulfilled, but the margin of failure was so small that the council agreed to go to the next step—i.e., to try to acertain the views of pathologists other than our own members.

The Association of Clinical Pathologists is, of course, only one, and the junior one at that, of the two main societies that concern themselves with pathology in Great Britain. According to its constitution the Pathological Society, our senior by twenty-one years, has as its object "to advance Pathology and to facilitate intercourse between pathologists". I am unable to see that this constitution in any way precludes the Pathological Society from expressing an opinion on the desirability of setting up some new organisation in pathology and even of participating in the project. The membership of the Pathological Society was circularised, and, although a much smaller percentage of their members voted, there was a fair measure of support and not much firmly expressed opposition to the proposal that something should be done. The Pathological Society includes so many more research and academic pathologists and overseas members that its point of view is not likely to be identical with that of the Association, but at least it was not in violent opposition. The council was therefore preparing to make further inquiries about the ways and means of achieving the desired result when a new and unforeseen complication—or perhaps simplification—emerged.

* * *

Shortly before the council was due to meet at the end of June, 1959, the chairman of council received a letter from the President of the Royal College of Physicians of London indicating that he was aware of the desire of pathologists to have an organisation of their own, and

accepting their complete right to do so if they so wished. He proposed, however, the alternative solution of a close liaison with the Royal College. Though he confirmed the improbability of any modification of the membership examination for the benefit of pathologists, he accepted the important and to us essential condition that under any arrangement pathologists would not find themselves in a position within the college inferior to that of physicians.

How then could doubts about equality of position be removed? Here I think we must give great credit to the President for realising that the college would have to be willing to demolish the barrier that made the previously suggested mastership in pathology unacceptable—namely, its failure to confer that privilege which alone testifies publicly the recognition of equality that is so earnestly desired. I refer, of course, to eligibility for election to the fellowship of the Royal College. And the President further professed his belief that, if accepted by the college and the pathologists, equality would be to the benefit of both branches of the profession.

Faced with this unforeseen new situation the council continued the working party under Professor Cunningham's chairmanship, and added to it the senior secretary of the Pathological Society as an observer. In the previous year—i.e., before the letter from the President of the Royal College had been received, the working party had already gone as far as it could in collecting information about the formation and financing of an independent college. Our inquiries had made it clear that a very large sum of money would be needed to found a college on even the most modest and economical scale, and that its running costs would be substantial. Pathologists by themselves could hardly provide it without crippling themselves by a permanent covenanted annual subscription of which my personal estimate is something substantially more than the figures in document B. Therefore some external source of money would have to be found. Given a case-iron case, perhaps it *could* be found. But before the council officially, or even individual members unofficially, could approach wealthy and philanthropic individuals or Foundations to solicit a substantial donation towards the formation of a college, it is essential to be able to proclaim that there is an overwhelming need for such an organisation and that the project commands the enthusiastic support of the great majority of those who practise that branch of medicine. Were these conditions fulfilled, there are avenues of approach that might be explored, but the council was not then and is not now in a position to make either claim. Although a considerable body of opinion favoured a college, this opinion had been obtained at a time when there was no alternative possibility in sight. The letter from the President of the Royal College introduced a new factor that had to be considered, and the working party—in my view rightly—proceeded first to formulate the essential requirements of pathologists that must be met by the Royal College of Physicians in order that the proposals might be subjected to detailed consideration and presentation to the members of the Association as an alternative to an independent college.

Accordingly negotiations have gone on in some detail and the results of these have been summarised in an agreed statement from the representatives of the Association of Clinical Pathologists and of the Royal College. From this it is seen that the representatives of the Royal College of Physicians are willing to recommend that there be set up within the college a faculty or division of pathology, the administrative control of which will be by a council elected by the members of the faculty, that admission will be by an examination controlled by the faculty with a generous provision for foundation membership, and that members of the faculty will be eligible for election to fellowship of the Royal College in the same way and by the same machinery as members of the college. The proposed accommodation for administrative and scientific purposes and the financial provisions appear to be satisfactory.

These proposals appear to me to be generous and to indicate a sincere and genuine desire on the part of the Royal College of Physicians to receive into their sodality the general body of pathologists in this country. It is for you to decide whether you wish to be associated with an ancient and honourable college with great prestige and influence, whose examinations are likely to receive immediate recognition, or whether you prefer to stand alone either to establish an independent College of Pathologists, with full realisation of the delays that this will involve both in setting up an examination and in obtaining recognition for it, or to refrain from action altogether, indifferent to the challenge of the future.

NOMENCLATURE OF ABNORMAL HÆMOGLOBINS

AT the eighth International Congress of Hæmatology, held in Tokyo last month, 44 members met to discuss the nomenclature of the human hæmoglobins. This field is expanding so rapidly that it is not possible even at an international congress to obtain a full representation of all disciplines and groups of workers. The absence of several distinguished investigators in this field was acutely felt. Nevertheless the congress was considered the best possible occasion for such a gathering. The following recommendations are being issued so that those not present will be able to criticise them in public:

1. The recommendations on nomenclature made at the Symposium on Abnormal Hæmoglobins in Istanbul in 1958, and published in 1959,[1] are endorsed and the letters A–N (with the exception of B), and S are recognised as naming hæmoglobins as there defined.

2. The description of the variants of hæmoglobin M as M_B, M_M, M_S (from Boston, Milwaukee, and Saskatoon respectively) is accepted,[2 3] and it is suggested that new hæmoglobins M are described with fully subscripted names until they have been shown to differ from these three when they should be given subscript initials (M_{Iwate}, possibly later M_I).

3. The letters O, P, and Q are being allotted to the hæmoglobins described under these letters.[4–6]

4. Until the next International Congress the letters R–Z (excepting S) should not be allotted to new abnormal hæmoglobins but these should be given names of localities. It should be left to the individual workers to choose the most meaningful name from the origin of the propositus, or the laboratory, hospital, town, or district where the hæmoglobin was found. A new name should not be allotted in this way unless it has been ascertained that the hæmoglobin to be named is different from all those adequately described in the literature.

5. Of the two designations of the hæmoglobin A_2 variant: A'_2 and B_2,[7] the first is found more acceptable. If a third variant should be found it should be named A''_2 and not C_2.

1. Abnormal Hæmoglobins; p. 387. Oxford, 1959.
2. Gerald, P. S. *Blood*, 1958, **13**, 936.
3. Pisciotta, A. V., Ebbe, S. N., Hinz, J. E. *J. Lab. clin. Med.* 1959, **54**, 73.
4. Lie-Injo Luan Eng, Sadono. *Brit. med. J.* 1958, i, 1461.
5. Schneider, R. G., Haggard, M. E. *Nature, Lond.* 1958, **182**, 322.
6. Vella, F., Wells, R. H. C., Ager, J. A. M., Lehmann, H. *Brit. med. J.* 1958, i, 752.
7. Kunkel, H. G., Ceppelini, R., Dunn, L. C., Firsheim, L. Cited by R. Ceppelini *in* Biochemistry of Human Genetics; p. 134. London, 1959.

6. The names of the three known peptide chains of human hæmoglobin are α, β, and γ,[8] and it is suggested that the normal chains should be designated in that way (i.e., not α^A or α^F, β^A, and γ^F). The genetic superscript for the normal gene product $^+$ (α^+, β^+, γ^+) will not be used as it implies to the chemist a positive charge.

7. The expressions β_4 for H and γ_4 for Bart's may be used when their identity is fully accepted. However, until the next International Congress the traditional names should be mentioned at least once in each publication.

8. The present custom to describe an abnormal chain by adding the name of the appropriate abnormal hæmoglobin in superscript should be maintained ($S=\alpha_2\beta^S_2$; Hopkins−2 $=\alpha_2$Hopkins$-2\beta_2$).

9. A polypeptide chain should not be designated with a new small Greek letter (such as δ and ε) until chemical evidence for complete separate identity from the α, β, and γ chains (such as exists between these chains themselves) has been established, genetic differences notwithstanding.

10. It is expected that the analysis of the aminoacid sequences in the globin molecule will eventually be followed by a precise chemical nomenclature. Meanwhile if a hæmoglobin has been identified by the usual methods of electrophoresis, chromatography, spectroscopy, alkali denaturation, cold denaturation, and solubility tests, it should be described by the accepted capital letter as hitherto: (S, C, D, G, E, &c.) as recommended by the Working Party meeting at the sixth International Congress in Boston in 1956.[9] If comparison has been made on the same lines and with the same completeness with a hæmoglobin carrying the name of a locality that name should be applied. If the abnormal chain is identified this should be indicated by a subscript; (for example: D_α, D_β) and until the full identity by examining the aminoacid sequences has been established this subscript should be followed by a declaration of origin ($D_{\beta\ \text{Los Angeles}}$, $G_{\alpha\ \text{Ibadan}}$). This implies that D_γ will have to be renamed $D_{\beta\ \text{Punjab}}$. If two or more of such hæmoglobins are then found identical by analysis of the aminoacid sequences, only the name of the hæmoglobin which was first discovered and fully defined by the conventional methods should be retained. For example, if $G_{\alpha\ \text{Ibadan}}$ and $G_{\alpha\ \text{Azuakoli}}$ are found to be identical regardless of which the aminoacid sequence has been fully examined first $G_{\alpha\ \text{Ibadan}}$ should be the remaining name. However, until the next International Congress the alternative names should be mentioned at least once in each publication.

11. No generally acceptable name was agreed upon for the familial condition in which hæmoglobin F persists into adult age without morphological changes of the red cells and without anæmia. The term non-microcythæmic thalassæmia was considered not specific enough as it might equally apply to the familial condition where hæmoglobin A_2 is raised without associated morphological changes. If the expression " high F gene " is used this should be done with reservation and only provisionally until further knowledge allows better terminology.

12. If several hæmoglobins are present the phenotype should be designated by listing the hæmoglobins in order of decreasing concentration regardless of genetical considerations (sickle-cell trait=AS, sickle-cell anæmia=SF, sickle-cell thalassæmia= SAF, or SFA, &c.).

MEDICAL DEFENCE UNION

THE Union, which last week celebrated the 75th anniversary of its foundation, now has over 47,000 members; and membership is increasing by about 1000 a year.

At the annual meeting on Oct. 4, Dr. S. COCHRANE SHANKS, the president, said that, experience having shown that claims against dentists were usually less expensive than those against doctors, the council had decided to reduce the annual subscription for dental members from £3 to £2. The Union's overseas indemnity scheme had been extended to cover practitioners anywhere in the world except the U.S.A. provided that they (1) had a qualification registrable with the General Medical Council or the General Dental Council, and (2) were on the register of the country in which they practised.

In 1959, 390 cases were referred to the Union's solicitors—a record number. There were 106 cases of alleged professional negligence. 11 were fought, and all but 1 were won. Of the remainder, 64 were abandoned, and 31 were settled by a payment made or shared by the Union. The same ratio as in previous years had been maintained—namely about 2 : 1 in favour of members. In court cases the ratio was about 10 : 1. During the year 1 out of every 17 members had applied for assistance.

Agreement had been reached between the three defence societies about the criteria to be satisfied when a member applied for assistance. A member's name would now remain on the Union's register for six months after failure to pay his subscription on the due date. Thereafter he would cease to enjoy the benefits of membership.

In 1959 the Union had been called on to deal with no fewer than 20 cases arising from failure to remove a swab from a patient's body. It had been decided in the courts that it was not sufficient for a surgeon to rely solely on the nurse's count but that he himself must take such additional precautions as were reasonable in the circumstances of the particular operation in order to minimise his dependence on the nurse's count. It was hoped that teachers in surgery would draw attention to this fact.

At a dinner held at Apothecaries' Hall on Oct. 4 to mark the 75th anniversary, the President responded to the toast of The Medical Defence Union, proposed by Sir Harry Hylton-Foster, Speaker of the House of Commons. Sir Russell Brain proposed The Guests, and Sir David Campbell responded.

8. Schroeder, W. A. *Progr. Chem. org. nat. Prod.* 1959, **17**, 322.
9. Lehmann, H. *Blood*, 1957, **12**, 90.

Public Health

Smallpox

MODIFIED smallpox has been diagnosed in a Dutch businessman who arrived at London Airport on Oct. 3 by flight BA 791 from Colombo, Ceylon. This man attended the casualty department of Charing Cross Hospital on Oct. 5, when he complained of an irritating skin eruption and was found to have a sparse rash. He was admitted to Long Reach Hospital, Dartford.

Those who travelled on the same flight as the patient have been traced. Those known to have been in contact with him since his arrival in England include, besides members of the staff and some patients at Charing Cross Hospital, members of the staff and a few prisoners at Wormwood Scrubs Prison, which he visited on Oct. 3.

Infectious Diseases in England and Wales

Disease	Week ended September			
	3	10	17	24*
Diphtheria	..	2	2	3
Dysentery	354	2	310	434
Encephalitis:				
Infective	3	2	4	..
Postinfectious	2	4	2	1
Food-poisoning	197	215	196	240
Measles, excluding rubella	1398	1156	1093	1501
Meningococcal infection	10	14	16	20
Ophthalmia neonatorum	22	20	24	15
Paratyphoid fever	6	6	13	9
Pneumonia, primary or influenzal	105	122	126	139
Poliomyelitis:				
Paralytic	9	5	13	3
Non-paralytic	7	7	3	5
Puerperal pyrexia	181	178	127	158
Scarlet fever	169	166	240	275
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	345	357	390	357
Meninges and C.N.S.	2	5	2	9
Other	53	42	46	54
Typhoid fever	7	6	2	6
Whooping-cough	1416	1376	1395	1132

* Not including late returns.

Conferences

BURNS

THE first international congress on burns was held in Washington, D.C., on Sept. 19–22 at the National Naval Medical Center, Bethesda. Prof. CURTIS ARTZ acted as coordinator. Of the 150 taking part, about a quarter came from countries outside the U.S.A. The members were welcomed by Dr. FRANK BERRY, Assistant Secretary of Defense and honorary chairman of the congress, who recalled his own experience in the treatment of burns—local ice water, local ambrine, local coagulants, exposure, and now back to ice water. The Surgeons-General of the Army, Navy, Air Force, and Public Health Service were also present.

There follow brief summaries of some of the contributions:

Dr. OLIVER COPE (Boston) analysed 106 fatal burns in 1141 consecutive cases treated at the Massachusetts General Hospital. Improvement in the past decade was chiefly reflected in prolonged life, not in overall survival. Respiratory damage accounted for 50% of deaths, and local sepsis was the second commonest cause.

Dr. NICHOLAS KETALIDES (Lima, Peru) reviewed the striking and well-known results obtained in Peru by use of oral saline in the treatment of burns shock. The results of saline alone seemed to be better than infusions with saline plus plasma, but the plasma therapy described would be considered inadequate by many people.

In a clear and carefully considered paper on sodium balance in burned children, Mr. A. D. R. BATCHELOR (Edinburgh) emphasised that during the early period of sodium retention considerable sodium loss could continue from the burn, and reduce the positive balance of the first two days. The later sodium loss during the period of separation of sloughs would be enormous and was well recognised.

For eleven years the Richmond Burns Center have used dextran in the treatment of severe burns and are well satisfied with it, Dr. B. W. HAYNES, Jr. (Richmond, Virginia), reported. There had been no hæmorrhagic complications, no anaphylaxis, and no increase of bleeding-time or clotting-time or change in prothrombin levels. Dextran seemed to restore cardiac output, as well as maintain circulatory volume.

A urologist, Dr. J. U. SCHLEGEL (New Orleans), made an interesting plea for the use of osmotic diuretics—e.g., 4% urea in 5% dextrose in water—to prevent renal shutdown. He emphasised the advantages of the bacteriostatic and bactericidal properties of urea in these patients.

Dr. FRANCIS MOORE (Boston) gave firm but qualified approval of 6% dextrose solution in the treatment of burns. It now formed 25% of colloid administered. Dextran raised the glomerular filtration-rate which was the chief factor in urinary volume. It was the tubules which determined the quality of the urine. The dextran-treated patient exhibited "solute diuresis", and Dr. Moore believed that this was undoubtedly beneficial.

Dr. H. A. FOZZARD (St. Louis) demonstrated that in experimental burns there was a true early cardiac insufficiency. This fall in cardiac output could be prevented by dextran and digoxin given together, but not by either separately.

Dr. A. MONSAINGEON (Paris) had studied tripeptidase activity in skin burns of intermediate depth, in the blister fluid, and in the plasma of both patients and rabbits. Tripeptidase levels in blister fluid and in plasma were comparable, and they returned to normal after the slough separated. A rise in tripeptidase activity at the site indicated deep sloughing. The method may help in therapeutic trials of anti-enzymes.

Dr. WILLIAM WARTMAN (Chicago) gave a detailed account of the postmortem findings in 41 patients dying of severe burns. They re-emphasised the importance of the pulmonary lesion and the multiple mechanism of death in most cases. 13 were classified as shock deaths, 5 were due to early gross lung changes, 16 to sepsis, 3 were attributed to gastrointestinal ulcers, and 1 to hepatitis.

Dr. F. B. HERSHEY (St. Louis) was interested in enzyme changes in the zone 2 (of Peters) and in the mechanism responsible for a 98% fall in oxygen uptake in skin exposed to 55°C for 60 seconds. He analysed the role of the Krebs cycle and of succinidehydrogenase in these mechanisms.

Dr. T. STENBERG and Dr. K. E. HOGEMAN (Malmo, Sweden) reported studies with ^{131}I-tagged rose-bengal in burned rats. Liver damage proportional to the extent of the burn was found, and was correlated with a decreased bile-flow. Similar changes were also found in burned patients.

The main impact of the papers on the first day was to emphasise the importance of pulmonary damage, and the need for tracheostomy in flame burns of the face, especially those incurred indoors. The value and general acceptance of dextran as a plasma-expander, and as a corrector of decreased cardiac output in the early stages, were clear. There was also general support for the use of solute diuresis by urea or mannitol in the prevention and treatment of early renal shutdown.

* * *

Dr. S. R. ROSENTHAL and others (Chicago) described evidence of the presence of toxins and antitoxins in the blood of burned animals and patients. Extracts of burned human skin inhibited Hela tissue-culture growth. This work suggested the possibility of producing antisera to toxic products of burned skin.

Dr. N. A. FEODOROV (Moscow) said there were changes in the antigenic structure of blood after burning. Specific autoantigens appeared in the blood of animals and man, similar to those constantly found in burned skin. These antigens were found in blood within 6–24 hours of burning. The blood cells of burned patients had antigenic properties against antitoxin of burns, and a therapeutic serum had been prepared which had prolonged and preserved life.

Dr. M. DOBNKOVSKY (Prague) had been able to correlate antigenic and biochemical changes in burned skin at various stages. Antibodies appeared between 4 and 8 days after injury.

Discussing disturbance of protein equilibrium after severe burns, Dr. T. G. BLOCKER and others (Texas) described dietetic needs, based on a study of 1000 burns and of the accelerated anabolism which ensued. 2·4 g. of protein and 45–90 cals. per kg. per day was recommended, plus potassium by enteric-coated capsules. The negative nitrogen balance was a matter of increased nitrogen turnover: the unsolved question was what drives this mechanism.

Dr. CARL MOYER (St. Louis), in an important study of vaporisation heat loss (V.H.L.), showed that this took place chiefly through blistered skin, but also through thick sloughs, and greatly accelerated the metabolic-rate. V.H.L. was more through skin than through lungs, and it could be checked by local cover, by immersion in a bath, or by use of a "fog room". A strong warning was issued by Dr. MOYER and Colonel E. J. PULASKI about the serious dangers of local abscesses and pyæmia when burns were covered by impermeable dressings. It was far safer "to pile on the fuel" until we had safe methods of controlling metabolism rather than use immersion or impermeable dressings, such as 'Cellophane'.

Dr. W. T. TUMBUSCH, Dr. E. H. VOGEL, and others (Texas) pointed to the rising incidence of pseudomonas septicæmia after burns. Of 740 patients, of whom 140 died, 63% had septicæmia, chiefly *Staphylococcus aureus* and pseudomonas, but with different clinical courses. Pseudomonas septicæmias were fatal within 12–48 hours, with hypothermia, leucopenia, and hæmorrhage; and *Staph. aureus* produced pyrexia, mental deterioration, and leucocytosis. There was a 50% mortality with *Staph. aureus* and 100% with pseudomonas.

Dr. KETALIDES and others (Lima) presented the results of 3000 cultures to show that antibiotics were ineffective against invasion by *Staph. aureus* or pseudomonas, but that gamma-globulin prophylaxis plus antibiotics significantly reduced septicæmia and death in young children.

Dr. S. M. LEVENSON and others (Washington) showed the decisive effect of previous sublethal total-body radiation (T.B.R.) on resistance to the shock phase of burns. This sensitivity was not specific to burns and extended to any trauma. Any surgery could be fatal if performed between the 6th and 12th days of T.B.R.

The highlight of the second day was the demonstration of a burns toxin and the possibility of producing an antitoxin. If these hopes are realised the mortality of burns could be dramatically improved. The work on vaporisation heat loss raises the prospect of eventual survival in 80–90% deep burns. The limitations of antibiotic therapy in countering *Staph. aureus* and pseudomonas invasion were underlined. The wider use of gammaglobulins seemed justified.

* * *

Mr. A. B. WALLACE (Edinburgh) was anxious to see the formation of an international committee, under W.H.O. auspices, to study means of preventing burns. Dr. MOYER said that there were 2 million burns a year in the U.S.A. with about 8000 deaths.

Mr. PATRICK CLARKSON (London) illustrated mortality-rates in England and Wales in 1949–59. These remained constant at 600–700 a year despite some improvements in therapy and prevention, and a big increase in burns centres. 20–25% were scalds; and 20–25% involved those under 15 years of age. Long-term improvement in prevention could come only from new housing with safe heating and no open-hearth fires. In London about 6 children per 150,000 under 15 were killed by burns per year. In the major cities of the Midlands and the north of England, where open-hearth fires were commoner, 30–50 children per 150,000 under 15 years were fatally burned in a year. Present fireguards were valuable but did not give complete security. The open-hearth fire should go.

* * *

At the Vyshnevsky Institute in Moscow burns shock was treated by pararenal block with procaine and by 1–3 litres of fresh blood or saline. Only burns of less than 10% were treated by excision and primary repair; other burns had the slough excised at the end of the third week, and were resurfaced by patch grafts, not sheets. Convalescent serum and corticotrophin were used for extensive burns with toxæmia.

Dr. J. G. CONNELL (New York) outlined successful rules of management for facial burns affecting trachea and lungs. These included prompt tracheostomy, enzyme aerosol, and repeated suction plus oxygen.

Mr. D. MACG. JACKSON (Birmingham) gave an authoritative account of primary excision and grafting—the most radical and logical, but potentially dangerous, treatment. No reduction in mortality-rates or healing times had been effected. The method may have advantages in expert hands for extensive burns involving fat, especially if they included the chest. The method was, of course, an enormous tax on the patient and fraught with special dangers in inexperienced hands.

Dr. W. A. ALTEMEIER (Cincinnati) pointed out the limitations of very early radical excision. 19 patients so treated had a 52% mortality; 35 comparable extensively burned patients treated along slower more conventional lines had a 51% mortality.

Dr. E. J. L. LOWBURY (Birmingham) recalled Colebrook's work demonstrating the effectiveness of local penicillin in protecting against injections of hæmolytic streptococci. Prophylactic creams containing neomycin, polymyxin, and hibitane could be almost as effective in the elimination of local *Staph. aureus* and pseudomonas infections, and the take of grafts improved significantly.

The proceedings of the congress will become a standard work of reference on burns for a long time to come. It was clear that the average standard of care to burned patients all over the world is vastly higher than it was ten years ago when the first symposium on burns was held in Washington. The therapeutic problem today is the routine salvage of the 40%-and-over deep burn, most of whom still die. The results are the same in most countries in the world. A breakthrough in more than one position is awaited—safe, quick, reliable methods of removing dead tissues, and the provision of stored antigen and free skin, are still lacking. Professor Artz has done a great service to this subject, and to all burned patients, in convening this congress.

PATRICK CLARKSON.

THROMBOSIS AND ANTICOAGULANT THERAPY

A SYMPOSIUM on this subject was held at Queen's College, Dundee, from Sept. 28 to Oct. 1.

Dr. J. R. A. MITCHELL (Oxford) demolished many cherished concepts of coagulation and thrombosis. Blood-clots and thrombi were entirely different in structure. The former were composed of all the blood constituents deposited in a homogeneous fashion, whereas the latter contained selective depositions of fibrin and platelets. Hence the demonstration in vitro of a factor which affected the one was no guide to its effect on the other. Evidence also indicated that generalised atherosclerosis, coronary atherosclerosis, coronary thrombosis, and myocardial infarction were not closely correlated.

Dr. J. C. F. POOLE (Oxford) endorsed these views and described an in-vitro method of producing "thrombus-like" structures by rotating blood in a closed plastic tube. The thrombus had a "white head" composed of platelets and a "red tail" of red cells. Heparin abolished the red tail, but not the white head, and the whole process was inhibited by short-chain fatty acids with upwards of 16 carbon atoms.

Dr. M. MATTER (Zürich) discussed the factors concerned in coagulation, and suggested that local changes in the vessel wall may be important.

Prof. H. W. FULLERTON (Aberdeen), describing work on the recalcified clotting-time (R.C.T.), stressed the need for meticulous technique. He had found that a high-fat meal accelerated the R.C.T., this effect being prevented in healthy people by activity. The acceleration was also prevented by phenindione in patients with either recent or long-standing myocardial infarcts.

Dr. S. NIEWIAROWSKI read for Dr. E. KOWALSKI (Warsaw) a paper which showed that fibrinolytic factors and coagulation are interrelated. For example, fibrinolytic agents not only digested fibrin but also inactivated factors V and VIII and released coagulation inhibitors.

Dr. A. S. TODD (Dundee) described an elegant method of placing tissue sections upon fibrin microfilms and observing the sites of fibrinolysis. He found that these were concentrated around blood-vessels, fibrinolysis being most active in the endothelium of veins, notably after damage to the cells. In thrombosed vessels fibrinolytic activity was localised at points at which the thrombus was not firmly attached.

Laboratory Control of Anticoagulant Therapy

Dr. H. HARTERT (Heidelberg), Dr. W. ZOLLINGER (Zürich), and Dr. W. WALKER (Dundee) described comparative studies of laboratory methods. The consensus of opinion was that thrombotest has considerable advantages over other methods.

Prof. P. A. OWREN (Oslo) said that in his view five categories of disorders deserved a high priority for long-term anticoagulant therapy. These were rheumatic heart-disease with emboli, angina pectoris of less than two years' standing, myocardial infarction, atherosclerosis in the lower limbs, and intermittent cerebral ischæmia. There were three groups of lesser priority —long-standing rheumatic heart-disease, angina pectoris of more than two years' duration, and repeated myocardial infarction.

Clinical Indications for Anticoagulants

Prof. R. B. HUNTER (Dundee) described the evolution of the present position with regard to long-term use of these drugs in myocardial infarction, and Dr. R. L. RICHARDS (Glasgow) reported a prospective clinicopathological study which indicated that in patients who had received anticoagulant therapy

on account of myocardial infarction necropsy evidence of thromboembolism was less common.

Mr. G. SMITH (Glasgow) suggested that anticoagulants were of value in thromboangiitis obliterans and in connection with endarterectomy for atherosclerotic stenosis in lower-limb vessels. He doubted their value for claudication per se except in so far as they might reduce the incidence of myocardial infarcts.

Dr. M. J. LARRIEU (Paris) described their use in orthopædic surgery to prevent thromboembolism.

Dr. A. C. TURNBULL (Dundee) showed evidence that anticoagulants are indicated after gynæcological operations in patients over 45 years, those who are overweight, and those with a history of thromboembolism or varicose veins.

Dr. A. BARHAM CARTER (London) and Dr. JOHN MARSHALL (London) discussed their use in cerebrovascular disease, and concluded that, although they introduced the hazard of cerebral hæmorrhage, they might benefit patients with slowly developing strokes and recurrent ischæmic episodes.

Heparinoids

Dr. NIEWIAROWSKI described the effect of heparin on blood-coagulation factors, and Dr. F. K. BELLER (Tübingen) and Dr. E. WINDSOR (Northridge, California) related experiences with new heparinoids.

Hæmatological Complications of Extracorporeal Circulations

Dr. A. A. SHARP (Oxford), Mr. N. G. ROTHNIE (London), and Dr. M. VERSTRAETE (Louvain) described how they found a fall in platelets and sometimes a decrease in fibrinogen content after perfusion—changes which did not appear to be aggravated by hypothermia. The most important factor in post-perfusion bleeding was insufficient neutralisation of heparin. 'Polybrene' was twice as effective as protamine, weight for weight, in the neutralisation of heparin, and must be given on the basis of the amount of heparin present before perfusion in a ratio of 1·5 to 1. The post-perfusion level of heparin was an inadequate guide, probably because extravascular heparin might subsequently return to the circulation. Active fibrinolysis might also occur after perfusion and may require the administration of fibrinogen.

Dr. J. MATZKE (Copenhagen) found that the severity of post-perfusion hæmorrhage correlated well with deficiency of antihæmophilic factor B and that such hæmorrhage could be controlled by administration of this factor.

Medicine and the Law

Too Drunk to Drive

THE law relating to drunken motorists is full of surprises. The Road Traffic Act, 1956, has a proviso probably intended to safeguard the motorist who, realising his condition, puts the ignition key into his pocket and gets into the back seat until he has recovered. It appears, however, that this proviso may cover less meritorious cases.

A 20-year-old garage mechanic drove his employer's breakdown lorry to a public house and with two companions set out to get as drunk as he could.[1] All three in fact became very intoxicated, and one of them—not the defendant—drove the vehicle back. The defendant was charged with being in charge of the lorry under the influence of drink, and was convicted by the local magistrates.

On appeal to quarter sessions, the conviction was quashed. The chairman of sessions explained that, although the defendant was in charge of the vehicle, there was a proviso that he should be deemed not to be in charge if circumstances were such that there was no likelihood of his driving the vehicle so long as he remained unfit to drive. "Although it is entirely unmeritorious, we think he is entitled to say that he was so incapably drunk that there was absolutely no likelihood of him driving this vehicle until he had recovered."

1. *Guardian*, Sept. 27, 1960.

In England Now

A Running Commentary by Peripatetic Correspondents

A DOCTOR in Scotland, after one or two unsuccessful applications for Highland practices, sent the local executive council the following:

Dear Sir,

There's no point in repeating the dreary recital of my career even if the Council was interested in it and if I do it too often I get writer's cramp and besides I'd really hate to bore them. There's nothing exciting to add to it anyway such as an expedition to the Amazon or a study of the incidence of onychogryphosis in Zanzibar; but I have done a three weeks locum here for Dr. ———— who will verify, if the Council cares to ask him, that I am not black but comely, sober, speak Italian, French, and English as well as Gaelic, and am popular with old ladies and that I could run a practice three times the size of the one you are advertising with competence and maybe even pleasure. You will understand that I am writing this to entertain and not in the hope that the Council, who will have more important things to do, will take it seriously. (I am assuming that they are familiar with the other great English humorists and also, which is maybe a larger assumption, that they can read.)

To digress a little, my last 5 years have been spent in a large industrial practice in ———— with a maternity turnover big enough to repopulate Hiroshima. I am as yet only a babe of 38. I know that this is a handicap and that I should be of pension age and maybe hold the world record for climbing palm trees in my bare feet or have done twenty years in Devil's Island. All I have is a lot of experience and what seems an insane desire for a small practice in the Highlands.

In case you fear the stream of communications will dry up, I shall be writing to you every time one of the Council's coy and solemn advertisements appear. I know they have to put them in to give people like me the democratic delusion that the best man might win. I doubt if I'll ever make much money with my pen if I keep on using it to apply for small country practices that are meant for other men than me—but as the Duchess said to the Bishop, "If you don't try you don't get anywhere".

Yours faithfully,

(Signed) ———— M.B., CH.B. (This doesn't mean anything—it's just where one of the hens came in and stamped in the ink.)

References:

(1) Dr. ———— Tel. ———— (Ring three times and ask for Nellie—surprisingly enough she might even answer.)

(2) Dr. ———— Tel. ———— (Ask for Peggy if Dr. ———— not in.)

(3) Willie the Weeper, Tanktown, New Orleans, U.S.A. — New Orleans 25634 (Ask for Shanghai Lulu and she'll ask for fifteen dollars.)

(4) S. J. Perelman — (Present whereabouts unknown).

The letter was "carefully considered" but he was not appointed. Sometimes I wonder if we should not have seen him.

* * *

When I left the public-health service to join the regional hospital board's administrative staff, I thought my stethoscope, often dusty, would soon gather cobwebs—but now I'm not so sure. Our offices overlook the city's main street, and in moments of relaxation we watch the suicidal tendencies of pedestrians compete with the homicidal urges of motorists, and the inspired dashes of old ladies with the determined lunges of public transport.

My first experience of our medical vulnerability came when an erring van skidded through the main window of our palace of fashion. Assisted by a host of excited typists I gave expert administrative attention to the driver, sitting pale and shaken among a collection of model gowns. Not long afterwards, an old lady took queer outside our main door and, acting on the magic word "hospital" which appears on our nameplate, came inside. As I happened to be passing at the moment I was asked to undertake the case. She had just been on a prolonged shopping expedition for wee tartan trousers for her only grandson; so a rest and a cup of tea did the trick, and I was able to retire with the mantle of Hippocrates about my shoulders.

By this time I was making a name for myself, and when I bathed the head of a small boy who had fallen off a bus, my reputation was made. Now sundry young ladies appear in my office with headaches, pimples, blisters, and splinters, and also ask my advice on halitosis, B.O., and shallow irregular sleep. One of our senior staff has shown me his psoriasis. I have had to assemble a first-aid kit, and my stethoscope, newly cleaned and polished, lies on top. Who knows, I might even get a chance to use it. My wife treats me differently, too. When I came home the other day with blood on my cuff, she gazed on me as she did years ago when, as a casualty officer, I regaled her with tales of horror and carnage. Last week she even let me bandage little John's finger instead of taking him to a real doctor.

* * *

My colleagues are always talking about their gardens, and I feel a bit out of it, since my own horticultural efforts have met with nothing but disaster. I planted some melon seeds once, for example, on blotting-paper. At first all was well. They grew so fast, indeed, that I took to leaving the door of my flat open in the morning so that they could spread themselves into the hall if they felt so inclined, rather than lift the roof off. It couldn't last, though. One day they outgrew their strength, or perhaps used up whatever nourishment they had drawn from the blotting-paper; I should have mentioned that it was green blotting-paper. Anyway, they lay down and died.

Next I tried some cactus seeds. I grew these strictly according to instructions, in a blue plastic tray of earth, and devoted much ingenuity to keeping them at a temperature of 70°. After weeks of observation, they came up. Unfortunately 25% of the crop was a weed, and 75% of the crop died.

My next experiment in propagation concerned an avocado pear. I wasn't sure of the structure of this exotic nut, so I cut the first one open to see whether there were lots of little nuts inside. There weren't; and, the price of avocado pears being what it is, I had to wait a year for another chance. My second nut has been planted for several months now. It hasn't actually sprouted yet.

Perhaps I should try something simple next—like mustard and cress, or a carrot top. I don't like to admit defeat though, especially since I read of a man who grows miniature Canadian redwood trees in pots.

* * *

I was returning by air from one of our Hebridean islands after making preliminary arrangements for the visit of a mass-X-ray unit. From the armchair comfort of B.E.A. I recalled with delight the tranquil pleasant way of life on that island and the charm of its people. Someone at the meeting had—regrettably—suggested giving donated prizes to lucky numbers to encourage attendance at the X-ray sessions and the idea was taken up with acclaim. When I left the story was sweeping the island that a tractor would be awarded to the thousandth person to be X-rayed. The Fiery Cross could not have spread the tale faster and I neither confirmed nor denied it. But I know that several bottles of whisky were donated, and it needed all my tact to decline an offer of 100 cigarettes as not being an entirely appropriate reward in this case.

* * *

In desperation we decided to take active and drastic measures to improve the abysmal standard of behaviour of the younger generation. An unyielding and consistent attack on the problem led to tears and bitter altercations, followed by, strangely enough, the playing of a gramophone, full blast through open doors.

I used to regard record-playing as a harmless, if perhaps rather strange, outlet for aggression directed against the parents. The children must know that it is now many years since we became totally immune to any amount of noise. But now I understand the significance. In times of stress and strife the record that is played is always the same. On one side is a bouncing *My old man's a dustman* and on the other side is a mournful *Fings ain't wot they used to be.*

Letters to the Editor

CHEMOTHERAPY IN CHRONIC BRONCHITIS

SIR,—The paper of Oct. 1 by Dr. Pridie and his colleagues is of great interest to us. In 1958, we asked the Ministry of Pensions and National Service to give us the names of people who had been certified unfit for work through bronchitis for more than a year in all, either continuously or for separate periods during the previous years.

The Ministry's local officers kindly sent out 188 letters to practitioners, as a result of which 91 patients were referred to us as outpatients. Physical disability or non-cooperation prevented completion of investigation in 18 cases, and, in the presence of conditions even more disabling than bronchitis, another 9 were excluded.

The remaining 64 severe bronchitics included 46 who had given up work more than a year ago, and 6 who had not worked for more than ten years. They formed as sad a group as we had seen outside wards for the chronic sick or mentally disturbed. Severely and continuously disabled, they rarely suffered the acute exacerbations which had so frequently punctuated their last working years. 35 of the group of 64 were unable to walk 100 yards slowly on the level (Fletcher's rating, grade-5 dyspnœa) and another 15 were so breathless as to be house-bound.

Waxed closed cardboard containers stored in the outpatient department were used for the collection of sputum specimens from these patients. These specimens were tested so as to select appropriate antibacterial drug treatment. After pancreatin homogenisation [1 2] the specimens were cultured on blood-agar plates (aerobically and anaerobically), and also on chocolate agar. The cultures were examined at 24 and 48 hours.

We found that *Hæmophilus influenzæ* was isolated in specimens from only 7 cases, whereas in 27 coliform organisms were predominant, and 30 yielded *Streptococcus pneumoniæ.* Many authorities are of the opinion that among bronchitics *H. influenzæ* alone or together with *Strep. pneumoniæ* comprise the aggravating organisms both in remission and in exacerbation.[3 4] We were therefore surprised to find that the sputum of our severe bronchitics yielded growths of *H. influenzæ* so seldom and of coliform organisms so frequently.

Nor did we find that, other than in 4 cases which were in exacerbation, treatment with penicillin V or tetracycline along lines commonly recommended led to any significant clinical improvement.

Our study leads us to suppose that among severe bronchitics treated intermittently in the past (as ours were) with antibacterial drugs, there may have been suppression of the usual bacterial flora, and consequent overgrowth of coliform organisms. These coliform organisms which are relatively resistant to antibacterial treatment may also have contributed to the lack of therapeutic response.

The Royal Hospital, Wolverhampton.

J. ASPIN
C. H. L. HOWELLS.

EXPERIMENTAL THYROIDITIS

SIR,—We were interested to read the article of Oct. 1 by Dr. Shepherd and his colleagues. Their results demonstrate, as did those of the Buffalo workers,[5] that following intradermal inoculation of thyroid extract there is no close relation between the occurrence of autoantibody and of thyroiditis. Our results, which were

1. Rawlins, G. A. *Lancet*, 1953, ii, 638.
2. Rawlins, G. A. *J. med. lab. Tech.* 1955, **13**, 133.
3. Mulder, J., Goslings, W. R. O., van der Plas, M. C., Lopez Cardozo, P. *Acta med. scand.* 1952, **143**, 32.
4. May, J. R. *Lancet*, 1954, ii, 839.
5. Terplan, K. L., Witebsky, E., Rose, N. R., Paine, J. R., Egan, R. W. *Amer. J. Path.* 1960, **36**, 213.

reported to the Pathological Society at Dublin in July, point to the same conclusion.

Using a similar technique in guineapigs, but giving repeated injections of thyroid extract, we were able to produce unequivocal thyroiditis in all of 15 animals which were followed for more than 150 days, but the antibody titre could not be correlated with the degree of thyroiditis.

There is now a good deal of evidence that the tanned-cell agglutinating antibody is not implicated in the causation of either experimental or human thyroiditis. It seems more probable that the antibody and the thyroiditis stem independently from some other initiating factor as yet unknown, or alternatively that the antibody is a direct consequence of the presence of thyroiditis. The latter suggestion would not be substantiated by the absence of antibody in the authors' experiment III, in which thyroiditis was produced by the injection of saline or adjuvant into one lobe of the thyroid. Similarly, we have recently found that thyroiditis induced in guineapigs by radioactive iodine is not accompanied by production of tanned-cell agglutinating antibody.

The parts played by the complement-fixing antibody, and by the cytotoxic factor described by Pulvertaft et al.[6] and Irvine,[7] are not yet clear.

It is difficult to understand why Dr. Shepherd and his colleagues failed to produce thyroiditis with a single intradermal injection of thyroid extract, as it has already been shown that thyroiditis can occur as early as 2 months after one injection.[5] Their suggestion that a simple saline extract of normal thyroid does not contain the required antigen is not borne out by either Witebsky's work or ours.

Departments of Pathology and clinical Pathology, University of Manchester. G. SCLARE
GEOFFREY TAYLOR.

SIR,—The paper by Dr. Shepherd and his colleagues describes the latest efforts to reproduce thyroiditis in rabbits artificially. It would be interesting to know whether, and where, experiment-minded pathologists or clinicians are considering the mechanisms by which prolonged oral treatment with thyroid in human cases of the disease, produces the slow, but steady and striking, reduction in the size of the goitre so that eventually the thyroid gland may be almost or quite impalpable.

Department of Pathology, General Hospital, West Hartlepool. R. T. COOKE.

THE "COST" OF SEPSIS

SIR,—The report of Sept. 24 from the Public Health Laboratory Service on the incidence of surgical wound infection was wisely cautious when estimating the monetary saving which would occur if postoperative sepsis were eliminated.

The tentative calculations were based on the false assumption that hospital costs are 100% variable—that is, hospital expenditure varies directly with its use. It is not surprising that the authors made this assumption, for it is made even in such authoritative economic analyses of the Health Service as the Guillebaud report [8] and in the accompanying publication by Dr. Abel-Smith and Professor Titmuss.[9]

The authors suggest that, if excess stay in hospital due to sepsis is 1,000,000 days per year, and if the average inpatient cost is £3·3 per day, then the annual monetary cost of sepsis is £3·3 million, and this could be saved by its elimination.

These calculations indicate a failure to understand the significance of the figure, £3·3 per day. The cost accountant produces it by dividing the total current expenditure of the hospitals (excluding those costs allocated to outpatient care) by the number of occupied beds. However, as I indicated recently,[10] nearly all hospital costs are overheads, or fixed, and they continue whether a bed is occupied or not. If sepsis is prevented, and a bed becomes empty, virtually no money is "saved". As the number of occupied beds (the denominator in the equation) has decreased, the only "monetary" effect is a rise in the inpatient cost per day! If the empty bed is used for a patient with some other disability, even this effect does not occur.

I suggest that expenditure on medical care is not causally related to the prevalence of diseases. It is usual to talk of the cost of sickness, cancer, &c., but this is only metaphorical. There is no expenditure on the abstraction "disease"—health expenditure occurs when such concrete entities as nurses and dentists receive incomes. The number of those providing medical care in a nation, and the size of their incomes, are determined by factors other than disease. These conclusions, although they may conflict with conventional views, can be verified by observation.

Richmond, Surrey. J. R. SEALE.

THE FEMALE PROSTATE

SIR,—"It is unfortunately still traditional for urinary symptoms in the female to lead to a gynæcological consultation . . ." So writes Mr. Thomas Moore,[11] and he is quoted with approval by Dr. Herzl Kook (Oct. 1). What exactly is this meant to convey? In my own hospitals I am glad to say that there is a free flow of patients in both directions between the urological and gynæcological departments, so that there is no backbiting between us.

The relationships of gynæcologists and urologists are such that they each need the other at times. There is no place for high-horse riding on the part of either of them.

London, S.E.21. PHILIP RHODES.

THE VERY DEAF CHILD

SIR,—May I comment on your annotation of Sept. 17, for I fear that some of the statements may mislead those readers who are not fully aware of the varying educational needs of children with impaired hearing?

Most teachers of the deaf do not regard as sacrosanct the definitions of the Board of Education's committee in 1938. Indeed, the National College of Teachers of the Deaf has been deeply concerned regarding the classification of deaf children, but teachers are aware of the difficulties in evolving a clearly defined system of classification which would meet the needs of all children. In point of fact the 1938 system has rarely been rigidly applied, the terms grade 2b and 3 have largely been used in an educational sense, and improvements in auditory discrimination have been realised and recognised.

You state that "non-auditory methods in special schools preserve the hearing loss of pupils unchanged". This shows a piteous ignorance of our schools. Group hearing-aids were in use before the 1939–45 war, and in recent years a great deal of valuable auditory training equipment of all kinds has been supplied, and is being used by children with all degrees of hearing impairment.

The last sentence of the article is jejune, and its implications are highly dangerous: it disregards completely the vital need to consider the child as an individual. How many children are, in fact, diagnosed "within the first few months of life"? What is meant by "adequate auditory stimuli"? Reference to the N.C.T.D. policy statement on the needs of the young deaf child will indicate the importance attached by teachers of the deaf to early diagnosis, parent guidance, and auditory training, but the selection of the most suitable educational environment is a complex and complicated problem involving numerous considerations in addition to hearing loss—powers of auditory discrimination, mental capabilities, lipreading abilities, communication skills, linguistic and emotional development, home background, and general educational attainments. It is of

6. Pulvertaft, R. J. V., Doniach, D., Roitt, I. M. *Lancet*, 1959, ii, 214.
7. Irvine, W. J. *J. Endocrin.* 1960, **20**, 83.
8. Cost of the National Health Service. H.M. Stationery Office, 1956.
9. Abel-Smith, B., Titmuss, R. M. The Cost of the National Health Service in England and Wales. Cambridge, 1956.
10. Seale, J. R. *Lancet*, Sept. 24, 1960, p. 696.
11. *ibid.* 1960, i, 1305.

paramount importance that all these factors should be taken into consideration when determining a child's educational future.

Longwill School, Birmingham. H. H. SHORROCK Headmaster.

SIR,—Mr. Gaskill (Oct. 8) does not appear to have read very closely either your annotation of Sept. 17 or the resolution from the Association of Non-Maintained Schools for the Deaf which is quoted in it: "Grade III deaf children are being placed in *Units for Partially Hearing Children* (my italics), a move which is detrimental to the education of the severely deaf child."

Mr. Gaskill ignores partially deaf units, each under the supervision of one or more teachers of the deaf, and concentrates entirely on the deaf child in the ordinary school. Full discussion of this would be out of place here but it should be pointed out that Mr. Gaskill betrays "a lamentable ignorance" of the auditory method, which depends, not on electronic apparatus, but on appreciating how the normal child learns to understand sound. The importance of the attitude of mind is especially brought out in the work of Wedenberg, who prefers to start without electronic apparatus merely by speaking close to the child's ear.[1]

I know of no-one who believes in merely placing the deaf child in an ordinary school "in the pious hope that by rubbing shoulders with hearing children they acquire speech automatically". Mr. Gaskill should give chapter and verse for this statement, and should also notify the previous advisers of the alleged failures of the auditory method.

Mr. Owen (Oct. 1) states that no-one has been able to formulate a classification with less defects and more practical advantages than that of the 1938 committee. The following classification [2] is a very slight modification of the one I learnt from Mr. Terence Cawthorne when I assisted him at the London County Council. It has been used for many years at the audiology unit of the Royal National Throat, Nose and Ear Hospital:

I Total Deafness.
II Subtotal Deafness.
Hearing for sound only.
No discrimination between speech sounds.
III Partial Deafness.
Hearing for speech sounds.
Ability to discriminate between:
(*a*) Vowels.
(*b*) Words.
(*c*) Sentences.
(1) Partially deaf—severe.
Words heard at less than 3 feet.
(2) Partially deaf—moderate.
Words heard at 3 feet or more: hearing-aid required.
(3) Partially deaf—slight.
Hearing-aid not required.

The advantage of this classification is that it gives information about the distances at which sound, speech sounds, and speech can be heard. It is a measurement of potential hearing—i.e., hearing before it is trained. The distance at which sounds and the voice are heard at initial testing gives an indication of the distance at which speech will be heard and understood once the child has learnt the meaning of the sounds he hears. This learning process is fundamental to the auditory approach and until it is understood sweeping statements will continue to be made about the "failures" of the method. The only "failures" of which I have personal knowledge of are due to neglect of the auditory approach at some point or other in the child's life.

London, W.1. EDITH WHETNALL.

1. Wedenberg, E. *Acta oto-laryng., Stockh.* 1954, suppl. 110.
2. Whetnall, E. Proceedings of Vth International Congress of Otorhinolaryngology, 1953.

SMOKING BY ADOLESCENTS

SIR,—May I endorse Dr. Fisher's letter of Sept. 24?

The time for kid gloves in dealing with this matter has gone; over twenty thousand deaths from lung cancer, a yearly sacrifice in this country, would, except for vested interests, compel instant action. At what figure will the Government act? A hundred thousand?

This self-destructive habit can only be squashed in adolescents by adult example. The other day I told a very young man that he was very likely planting the seeds of cancer of the lung, also of coronary disease and bronchitis, by smoking many cigarettes now and that they might foully blossom when he was forty. He answered: "Quite candidly I don't care a damn what happens to me when I am forty"; the time of nemesis was too incredibly remote to deter him; that is as it should be, if a youth has long foresight and prudence there is something wrong with him.

It is the adults who stand indicted of mass murder by example. From the physical side there is not a single thing to be said in favour of tobacco-smoking, and it is the adults' and especially the doctors' responsibility to save adolescents by example.

Beckley, Rye. C. G. LEAROYD.

ALL CYCLES ARE NOT MENSTRUAL

SIR,—Your leader of Oct. 1 on cyclical œdema and shock, which discusses the interesting case reported at length by Clarkson and his colleagues,[1] follows them in a curious error which deserves a little discussion.

They noted in their patient a "striking relationship of her shock episodes to the menstrual cycle", by which they mean that when she got an attack of œdema and vascular shock it was usually near the time of menstruation. From this they concluded that the recurrent attacks were in some way caused by the menstrual cycle and should therefore cease if hysterectomy and bilateral oophorectomy were carried out. Unfortunately the attacks recurred after the menopause produced by these operations, which thus experimentally disproved their hypothesis. In spite of this, they cling in their discussion to the idea that menstruation "in some ill-defined way exerted a powerful modifying influence, unveiling an underlying disease process", and all the papers they seem to have consulted in the literature are concerned with aspects of menstruation.

You follow them in this. You and they seem to disregard the considerable literature which exists on cyclical recurrent physical and mental illnesses, even those with a cycle of about 28 days independent of the menstrual cycle. Such illnesses are seen also in men, may continue into old age in both sexes, and when carefully recorded for a year or two in younger women can be seen running slightly and variably out of phase with the menstrual cycle. Reimann [2] reviewed a number and described some of his own cases under the title of "periodic disease"—cyclic fever, œdema, arthralgia, and neutropenia (see his fig. 1). Richter [3] likewise has collected many cases, while others [4 5] have made interesting steroid studies in their pathological analysis (see also Lingjaerde and Bredland's [6] fig. 1).

Cyclic processes are facts of pathology as of physiology and multiple rhythms occur in the single individual throughout the evolutionary tree. This knowledge does not seem to have penetrated clinical medicine in the way it has gained acceptance in the rest of biology, perhaps because so little is known of the underlying mechanisms of cyclic illnesses. But at least a menstrual mechanism can usually be ruled out.

In any event I think Dr. Clarkson and his colleagues were guilty of rather careless thinking. Their patient's attacks

1. Clarkson, B., Thompson, D., Horwith, M., Luckey, E. H. *Amer. J. Med.* 1960, **29**, 193.
2. Reimann, H. A. *Medicine*, 1951, **30**, 219.
3. Richter, C. P. *Recent Progr. Hormone Res.* 1957, **13**, 105.
4. Hokfelt, B., Luft, R., Sekkanes, J. *Acta endocr. Copenhagen*, 1959, **32**, 411.
5. Bondy, P. K., Cohn, G. L., Herrmann, W., Crispell, K. R. *Yale J. Biol. Med.* 1958, **30**, 395.
6. Lingjaerde, P., Bredland, R. *Acta psychiat., Kbh.* 1954, **29**, 355.

occurred up to 6 days *before* or 3 days *after* the onset of menstruation (in one instance 14 days after the onset), and as every endocrinologist knows *before* and *after* are two quite different biochemical situations: it is not very likely that both could give rise to œdema and shock. Surely we should expect a more precise time relationship than this between illness and menstruation, if we are to assume a physiological link and not just a coincidence.

One of the important positive findings of their work is, in fact, that the sexual cycle was not responsible for the regularly periodically recurrent illness. If in the future we can avoid the hasty assumption that all cycles must be menstrual, more progress would be made in understanding and treating these curious cases.

All Saints Hospital,
Birmingham. J. L. CRAMMER.

*** In summarising the paper by Clarkson and others we noted the association with menstruation, but in our later comments we agreed with Dr. Crammer that the fluid retention associated with menstruation could not have been the primary cause of this patient's œdema. On the more general question of cyclical disorder, we referred to the paper of Rogers,[7] which brings together much evidence of a menstrual periodicity in various diseases.—ED. L.

SIDE-EFFECTS OF LIBRIUM

SIR,—We have read with interest and concern the letter of Oct. 1 by Dr. Ingram and Dr. Timbury. We agree with their conclusion that this drug should be used with circumspection and scepticism, since we believe that this attitude should be adopted when any new psychopharmacological preparation is being investigated. In addition to the report of Breitner,[8] which records improvement in all 7 cases of "obsessional states", five other workers in this field have published interesting results.

English[9] treated 87 patients with 'Librium' and states that he has found it to be effective in obsessive-compulsive disorders without producing excessive sedation. Bowes,[10] in over 200 patients, finds this drug to be a significant advance in the treatment of anxiety states, and further, that it is effective in longstanding anxiety and phobic reactions and some obsessional states. Tobin,[11] who was quoted by Dr. Ingram and Dr. Timbury on side-effects, stated in the same paper that of the 27 patients who exhibited obsessive thinking and compulsive behaviour, 23 derived some degree of subjective improvement. Voelkel[12] claimed a favourable response in mild phobic reactions to a dose of 10–30 mg. daily. Garrone,[13] in a series of 180 psychiatric outpatients, reported a good response to librium in those patients with obsessional symptoms.

In Dr. Ingram and Dr. Timbury's series of 15 cases of phobic anxiety states and obsessional neuroses, an improvement in 4 cases is considered disappointing and is of doubtful significance. The corollary of this is that, apart from drowsiness in 7 out of 15 cases, the incidence of the other side-effects reported cannot be considered significant.

In our own experience with this drug in over 50 cases in psychiatric hospital patients and outpatients, the only side-effects occurring regularly are ataxia and drowsiness. Ataxia generally develops after several days' treatment and usually with doses of 50 mg. daily and upwards. In outpatients this may be seriously inconvenient or dangerous. In contrast, the drowsiness is often greatest in the first few days of treatment and may disappear without reduction of the dosage. In degree it is similar to that with which we are already familiar when using phenothiazine compounds.

Against this we have found the response to librium in obsessive-compulsive disorders and anxiety states to be distinctly encouraging, and we hope to publish results to substantiate this at a later date.

Herrison Hospital,
Dorchester, Dorset. A. G. FULLERTON
M. S. BETHELL.

SIR,—I wish to welcome Dr. Ingram and Dr. Timbury's suggestion that librium should be used with circumspection. I have used this substance since April, 1960, in the treatment of 200 patients, and I am able to confirm its usefulness in the treatment of phobic and obsessional symptoms.

The doses given to neurotic patients never exceeded 30 mg. daily in divided doses. As there is a tendency towards cumulative effects, this dose may be reduced after the first or second week. The main side-effect seen in patients so treated was drowsiness. None of the side-effects described by Dr. Ingram and Dr. Timbury were observed in my neurotic patients.

In the treatment of psychotic or psychopathic patients larger doses are necessary, the maximum doses reached in such patients has been 150 mg. a day. In only 3 patients paradoxical side-effects like irritability and aggressiveness were observed.

In the trial carried out at this hospital, librium has been found to be a valuable drug in the treatment of both neurotic and psychotic conditions, and side-effects can easily be avoided by observation of dosage recommended by the makers.

Long Grove Hospital,
Epsom, Surrey. JOHN DENHAM.

SIR,—Moved by the considerable public relations and advertising campaign, I decided to try using librium to allay anxiety in patients attending an N.H.S. general dental practice.

At first I thought the problem was a simple one of giving capsules to obviously frightened patients. Thought convinced me that it is very difficult to assess a drug responsibly in the public forum, when so many factors other than the drug are at work.

The attitude of the dental surgeon is important in reducing anxiety in dental patients. A process of unconscious selection of patients by the dentist could operate. Some practitioners may attract more very anxious patients than others. The more obtuse of us may not notice that patients are anxious. Most dentists must notice that variation in their own mood causes variation in the degree of apprehension shown by patients.

Dentists also vary in their assessment of a drug according to their job. A practitioner wants a drug that works with the minimum of inconvenience (cyclopropane is an excellent example of a drug that many dental practitioners dislike because of the protracted after-effects, yet its efficacy cannot be denied). On the other hand, a dental consultant needing to project a "brand" image of progress and advanced ideas might tend to ignore side-effects which do not matter much in a hospital.

I felt it necessary to elaborate on this question of user bias since it is extremely difficult to assess whether librium has been effective in the circumstances in which I have used it.

Out of 200 patients being treated at the time, I found only 15 whom I thought would benefit from librium. 6 were children who resisted treatment.

Each child was given librium $1^1/_2$–2 hours before the appointment (1×10 mg. capsule). In 4 children, ages 4, 5, 6, and 8 years, the results were dramatic. Crying, fighting children became cheerful and cooperative. The 5th child did not respond. The 6th child was a mental defective aged 8 years and did not respond to 2×10 mg. 2 hours before the visit. One child was tired and drowsy, obviously as a result of the librium.

The main difficulty in summing up the effect of librium on children is that giving a child a drug may well relieve the

7. Rogers, J. *New Engl. J. Med.* 1958, **259**, 676.
8. Breitner, C. *Dis. Nerv. Syst.* 1960, **21** (suppl. 3), 31.
9. English, D. C. *Curr. therap. Res.* 1960, **2**, 88.
10. Bowes, H. A. *Dis. Nerv. Syst.* 1960, **21** (suppl. 3), 20.
11. Tobin, J. M. et al. *Dis. Nerv. Syst.* 1960, **21** (suppl. 3), 11.
12. Voelkel, A. Paper read at a Symposium held by the German Neuropharmacological Association, Nürnberg, April, 1960.
13. Garrone, G. et al. Paper read at a Congress of Neuropsychiatry, Barcelona, 1960.

tensions of a parent who anticipates a scene. The resulting mood change in the parent then produces a cheerful child. This makes the attribution of the cause of the child's good behaviour an uncertain matter.

9 adults were given librium. 3 were noticeably less apprehensive at their second visit. The difficulty here is that many patients are much more agreeable at the second visit. Patient and dentist have got to know each other a little, the lion has been bearded in his den (the patient's angle), and the fact that the patient has returned means to both a tacit admission of at least a degree of trust.

I had one unexpected result. To one patient I gave 3×10 mg. capsules, 2 to be taken at 11.30 A.M. (for a 2 P.M. appointment) and 1 at 6 P.M. He slept for the succeeding 3 days, only getting up for meals. However, he had lost quite a lot of blood, and I suspect had also taken a whisky or two (or three probably), and that this was a case of alcohol potentiation, though he would not admit that the responsibility for his stupor was his.

The manufacturers' literature contained ample warning of side-effects, and a covering letter from the medical adviser contained a specific warning against alcohol potentiation and against driving after taking librium.

Salisbury. HUGH V. CAPSTICK.

SIR,—I read with interest the letter by Dr. Ingram and Dr. Timbury in which they reported results of treating 15 hospital outpatients with librium. Their findings contrasted so strongly with my own experience of this drug that I felt impelled to describe the preliminary results with this drug in some of my own patients.

Over the past three months I have used librium in a number of neurotic patients (25–30) seen in general practice, but up till now I have detailed notes and adequate follow-up observations on only 16 of them. The conditions treated included anxiety depressions and other psychoneuroses, phobias, chronic alcoholism, and chronic depression, the main symptoms being anxiety, tension, and insomnia. Some of these patients had been treated with a number of other drugs, without much success. The usual dose was 10 mg. three times daily, but doses of 60 mg. daily were sometimes given. The duration of treatment varied from ten to forty days.

The results showed that 80% of these patients responded well, and symptoms were usually relieved within five to ten days. In some cases, the effect of the drug was truly spectacular. In 3 patients, it was possible to suspend treatment after seven days, without relapse.

Regarding side-effects, the only ones complained of have been slight drowsiness (3 patients) and mild constipation (1). In none of them was it necessary to suspend treatment. I have been so impressed with the effect of librium that I am now extending the present trial to include a larger series of patients and I shall hope to publish detailed findings later.

It is likely, of course, that Dr. Ingram and Dr. Timbury's patients were more severely ill than mine and the higher doses used by them may have explained some of the side-effects they reported. Nevertheless, it is hoped that my experience will encourage other general practitioners to try librium in the milder psychoneuroses so commonly met with in general practice.

Leek, Staffordshire. G. KAGAN.

SIR,—I have treated 15 patients with librium and only 2 have complained of side-effects. Both were receiving 30 mg. daily and complained of drowsiness. In addition to drowsiness, one of these patients also complained of apathy. These side-effects persisted in a reduced dose of 20 mg. daily, and the drug was discontinued. So far my impression is that librium is most useful in treating the moderate anxiety state with tension which is more commonly found in general practice.

London, W.1. J. B. VERGANO.

ASSESSMENT OF HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—There may be others like me who are afraid to confess it, but may I state that I can rarely feel the normal liver through the abdominal wall? In view of the similar consistence of raw liver and steak, I am not surprised. The palpability of the liver depends more on consistence than size. As a control I have frequently got my surgical dressers at laparotomies to try to feel through the abdominal wall a normal liver which they have seen extending well below the costal margin, but they have never succeeded in doing so. Is the frequency with which physicians state they can feel the normal liver merely an expression of their lack of opportunity of controlling their observations?

London, W.1. DAVID H. PATEY.

SIR,—Mr. Grimshaw (Oct. 8) rightly draws attention to the value of palpation at laparotomy as a means of avoiding a possibly useless resection of primary malignancy. May I add a plea for an even simpler preliminary manœuvre? Laparoscopy, through a $^1/_2$ in. incision under local anæsthesia, permits visual inspection of the liver surface; secondary deposits are unmistakable, and when seen will eliminate, by the same reasoning, the need for a major incision to admit the palpating hand. This examination, performed as a routine in many centres on the Continent, often as an outpatient procedure, deserves to be more widely practised in Britain.

London, W.1. BRIAN STANFORD.

PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—The letter of Sept. 24 by Mr. Lane Roberts was of considerable interest to me since an attempt to elicit the physical sign which he described in doubtful cases of perforated peptic ulcer has been used by me for many years. I normally elicit this sign by grasping the pelvis on both sides and then rocking the patient gently from side to side. Like Mr. Lane Roberts I have found this sign of great help in differentiating between acute appendicitis and a perforated duodenal ulcer, but in spite of many attempts to elicit it in the conscious patient I have always failed. Herein lies the limitation of peritoneal splash as a physical sign; one must await the arrival of the anæsthetised patient in the operating-theatre before it can be elicited. Furthermore, only a positive result is of value; with a negative result doubt remains.

University Department of Surgery,
The General Infirmary, Leeds. F. G. SMIDDY.

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—The 10 patients treated with Dr. Mooney and Dr. Heathcote's vitamin-B_{12}/peptide complex are identical to those referred to in a previous letter.

In 4 the dose was reduced to 20 μg. In 2 of these patients (W. R. and S. K.), there was a recurrence of macrocytic anæmia, and in 1 (S. K.) signs of subacute combined degeneration developed. A 3rd patient (A. A.) did not lose the feeling of fatigue and reach her highest hæmatocrit values until after being transferred to parenteral therapy. Patients maintained on daily doses of 100 μg. suffered no hæmatological relapse—only a decline of the serum-vitamin-levels—during the period of observation.

The microbiological assay of serum-vitamin-B_{12} concentration is extremely useful as an objective estimate of the degree of vitamin-B_{12} deficiency [1] and we feel that cases of pernicious

1. Herbert, V. The Megaloblastic Anæmias; p. 82. London. 1959.

anæmia successfully treated should have serum levels within the normal range. A decline to low levels is almost certainly the forerunner of a hæmatological relapse.

The object of Dr. Mooney and Dr. Heathcote's paper did not escape us, yet we felt it necessary to point out how important it is to check the serum levels of the vitamin whenever an oral preparation is used—especially when the doses recommended for maintenance therapy appear to be inadequate. Finally it goes without saying that we do vitamin-B_{12} estimations as an accessory and not as a substitute for blood-counts.

City General Hospital, Sheffield. S. VARADI.

TROLLEY-SETTING

SIR,—May I give a further personal reassurance to Dr. Behr (Sept. 17) that an examiner of the General Nursing Council views with pleasure the advent of methods which will simplify the practice of aseptic technique, while making it safer for the patient.

The introduction of a sterile supply service must certainly bring changes in nursing procedures. The emphasis on the technical aspect of "trolley-setting" will disappear, I hope, and there will be more time and effort spent in learning the skilful practice of procedures.

Relieved of the time-consuming chores of the older methods, the nurse should have more opportunity to develop the art of that nurse-patient relationship about which we talk so much and practise too little.

The General Hospital, Northampton. MARGARET J. COOPER Principal Sister-Tutor.

CHOLERA IN AFGHANISTAN

SIR,—You mention (Sept. 3, p. 544) "direct air communications" between Quetta (Pakistan) and Kandahar (Afghanistan). May I draw your kind attention to the fact that there is no direct air connection between these two towns, though both these border towns have airports? Kandahar is directly reached by air from Karachi, Teheran, or Kabul.

Direct traffic between the two border towns goes by land: a railroad leads from Quetta to New Chamam on the Pakistan side of the Khojak Pass, some 85 miles northwest from Quetta. From Chamam to Kandahar the distance is 65 miles by good road.

The most convenient entrance to Afghanistan from the East and by surface is through the Khyber Pass from Peshawar along a road which is motorable all year though bad in spots beyond Djelalabad inside Afghanistan.

It is more likely that cholera spread by surface via the land routes from Pakistan to Afghanistan, especially since there is a continuous traffic of camel caravan in both directions throughout the year.

Karachi. F. E. PERABO W.H.O. Senior Adviser.

PROCHLORPERAZINE IN THE PROPHYLAXIS OF MIGRAINE

SIR,—Prochlorperazine ('Stemetil') is 1-(3-(2 chloro-10-phenothiazinyl)propyl)-4-methylpiperazine and belongs chemically to the phenothiazine group. It was given to 54 patients with typical hereditary migraine and no other important diseases. All were known to me because of earlier treatment, following the usual principles with differing results.

1 tablet (5 mg.) of prochlorperazine was given three times a day. Patients with rare attacks have been under observation longer than those with more frequent ones in order to obtain a reasonable judgment of the prophylactic effect of the drug. Observation time varies from one to four months.

A "good" result (practically total relief of symptoms) was achieved in 17 cases and "improvement" (a substantial reduction of symptoms) in another 17. The remaining 20 were unchanged. In treatment with placebos I have achieved a "good" result plus "improvement" in 25% of a similar group of patients.

With prochlorperazine 2 patients complained of a certain apathy and another had a rash.

Frederiksberg Hospital, Copenhagen. T. DALSGAARD-NIELSEN.

FATAL RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—Dr. Pryer and his colleagues omit the most pertinent comment in their report of Oct. 1. This in my opinion should be a condemnation of the almost universal and unnecessary habit of inflating the cuff of endotracheal tubes in ordinary cold-list cases. Even when respiration has to be assisted, a no. 9 tube fits so snugly into a woman's trachea that the small leak acts as an accessory expiratory valve.

St. Bartholomew's Hospital, Rochester, Kent. P. AZZOPARDI.

Obituary

THOMAS BAILLIE JOHNSTON

C.B.E., M.D. Edin.

RENOWNED as anatomist and medical administrator, Prof. T. B. Johnston was associated for nearly thirty years with Guy's Hospital and its medical school. His prodigious services, first as dean of the school and then as superintendent of the hospital, stamped his own mark of quality on the character and work of both institutions. He edited *Gray's Anatomy* from 1928 to 1958.

Born in 1883, he qualified, like many fine anatomists, in Edinburgh—in 1906, with first-class honours. He was demonstrator and lecturer in anatomy in Edinburgh until 1914, when he was appointed to a lectureship at University College, London. He served in France and Italy in the R.A.M.C. during the 1914–18 war and was mentioned in despatches. Then in 1919 began his long association with Guy's when he was appointed to the University of London chair of anatomy. His executive skill was outstanding, and so rapidly did he win the esteem of new colleagues that only a year later he became dean of the medical school.

Vandyck

His success at this difficult time, when the number of students was greater than it had ever been, was the first of many in a memorable deanship. The trials of the early days are recalled by J. J. C.:

"When Johnston first came to Guy's the medical school buildings were quite inadequate for a large undergraduate teaching school. The only funds available were students' fees and a small endowment income. The anatomy department was in a ramshackle single-storey building of uncertain age, which might have been suitable as a store-room or a large public lavatory but certainly not as an anatomy department. The department of pathology and the postmortem room were in a converted warehouse widely separated from the wards, outpatients, and medical school. And no long-term policy had ever been devised for the school.

"Johnston early saw that much had to be done, but in the conservative atmosphere of Guy's progress had to be by infiltration rather than frontal attack. Fortunately he had qualities which quickly dispersed suspicions that a stranger

from north of the Tweed might have aroused. His broad vision and quick appreciation of problems, his well-balanced judgment and friendly attitude, enabled him to complete his plans relatively quickly. A few years after his appointment a new anatomy department was built; and soon a new constitution, drawn up by Johnston, was adopted for the medical and dental schools and has proved its value over the years. Some ten years later a new pathology department, amply provided for teaching and research, was opened. Few of the present generation realise how much Guy's owes to his drive and vision."

In 1938 Johnston took on the new role of superintendent, at the urgent entreaty of the governors and particularly of his friend, Lord Nuffield, treasurer of the hospital. Again he faced troubles, and J. J. C. continues:

"The financial situation in 1938 had reached a crisis when any day there might be no money in the till to pay the hospital staff. Both officially and unofficially, Johnston tried all he could to get help from the London County Council and the Ministry of Health, but it was in fact the disaster of the war in 1939 and the formation of the Emergency Medical Service that retrieved the situation. Johnston was appointed group officer for sector X, a post which he held until the end of the war. In his headquarters, a large and cold Victorian house near Orpington Hospital, he had to perfect the organisation for dealing with casualties; and he was also responsible for the posting of medical personnel to the various sector hospitals, a difficult and invidious task. He worked during bombardment from the air, slept in dugouts, watched the Battle of Britain, and arranged the disposal of wounded from Dunkirk.

"After the war he returned to Guy's as superintendent. Much work awaited him: all the wards in Guy's House had been empty since 1939 and there was heavy damage from fire and bombs. After two busy years, he retired just before the start of the National Health Service.

"He was a bachelor and for long lived in or near Guy's. He entertained a great deal and his hospitality was famous, for he was a perfect host, who planned every detail for his guests' enjoyment. In his younger days and well into middle life he was a keen player of squash and lawn tennis. For nearly forty years he was a member of Huntercombe Golf Club, where he quickly won the close friendship and respect of Lord Nuffield, whose many generous benefactions to Guy's were probably to some extent inspired by his confidence in 'the Dean'.".

Of his work as an anatomist, D. V. D. writes:

"Despite ever-increasing administrative duties, Johnston's interest in antomy never waned. He was a keen member of the Anatomical Society and published several papers in the *Journal*, mainly on embryological topics. He was, with his old friend, T. B. Layton, the second oldest member of the society. He became vice-president and, after his retirement, was elected a life member. He was a British delegate to the International Congress of Anatomists, in Milan in 1936. With A. F. Dixon and E. B. Jamieson, he presented to the society in 1933 the revised anatomical terminology, now known as the Birmingham Revision. This was to be submitted to an International Congress of Anatomists but the opportunity did not come until 1950 when Johnston, with G. A. G. Mitchell, was appointed secretary of the International Anatomical Nomenclature Committee which reported in 1955. The whole process took over twenty years and to it Johnston devoted much time and hard work. He lived to see the new terminology adopted and even incorporated in his own works. He resigned from the standing subcommittee only about a year ago.

"In anatomy Johnston was best known as editor of *Gray's Anatomy*, a task which brought him contacts with medical men the world over. About 1928 F. G. Parsons, of St. Thomas's, was consulted by Longmans Green about an editor for Gray, to work with and succeed R. Howden. Parsons suggested Johnston, who met Howden on one of the latter's visits to the General Medical Council. The meeting did not go well and ended in Howden resigning from the editorship, leaving Johnston to take on the job. Like most Edinburgh men, Johnston had been brought up on Cunningham, and had never read Gray. In the next two years, however, he revised it and entirely rewrote the section on embryology, which remains as an example of the precision and clarity of his work. He edited Gray for ten editions and held the reins until the centenary edition of 1958. For several editions he managed on his own, but later had the assistance of James Whillis and Frances Davies, each of whom in turn joined him in the editorship. I joined them on the tragic death of Whillis and was soon to learn how kind and helpful T.B. could be, while paying meticulous care to every detail. I shall always be grateful for the careful, considerate, and methodical training he gave me. For T.B. nothing but the best effort and work was adequate for Gray.

"His *Synopsis of Regional Anatomy*, first published in 1921 when he was at the height of his powers as a teacher, has also served generations of students. Its latest edition, the eighth, appeared in 1957, nearly ten years after his retirement from the chair—adequate testimony to its quality and usefulness.

"We mourn the passing of another of the great gentlemen of anatomy, but his name will live in the pages of the book he came to love so well."

JOHN TYRER JOHNSON

D.S.O., M.D., B.Hy. Durh., D.P.H.

Colonel John Tyrer Johnson died at Wooler, Northumberland, on Oct. 5, aged 82.

He was born at Newcastle upon Tyne and qualified with honours at Durham University in 1899. He volunteered for service in South Africa and later obtained a permanent commission in the R.A.M.C. He served in Korea in 1903 and in China during the Boxer Rebellion. During the 1914–18 war he was awarded the D.S.O. in Gallipoli, where he was the D.A.D.H., and also won the Order of St. Sava of Serbia. After the war he became successively A.D.H. at Aldershot, A.D.M.S. Meerut District, Senior Medical Officer, Gibraltar, and finally D.D.M.S., Egypt and Palestine Command.

After his retirement from the Army Medical Services in 1933 he went into general practice in Guildford and later became deputy medical officer of health (casualty services) in Guildford just before the outbreak of the last war. When the war began he rejoined the R.A.M.C. as a lieut.-colonel and served throughout the war as senior medical officer of the Royal Arsenal, Woolwich. For some years afterwards he was chairman of pensions appeals tribunals and travelled all over the British Isles.

For the last ten years he had been enjoying a happy retirement in Scotland, and he returned to his native Northumberland only a few weeks before he died. Tyrer Johnson is survived by his second wife and his daughter by his first marriage.

ARNOLD AUBREY WATERMAN

B.A. Cantab., M.R.C.S.

Dr. Aubrey Waterman died at St. James' Hospital, Balham, on Sept. 22 at the age of 42.

He came to England from Trinidad during the war and studied at Cambridge and at Guy's Hospital. After qualifying in 1951 he held a number of hospital appointments, including a medical registrarship at the National Temperance Hospital, before settling in general practice in Tooting. D. McW. writes: "Aubrey Waterman was eminently suited both by training and temperament for general practice, for he had treated the sick of every colour and social class for a wide variety of illnesses. He treated them all with unfailing thoroughness and compassion, and they soon found themselves at ease with one whose gentleness contrasted strikingly with a powerful physique and strength of will. He was dedicated to his work but far from pompous about it. His humour was ready and often ribald, and his devotion to medicine was almost equalled by his passion for music. In this, too, he was devoid of intellectual pride and he was thus able to share his enthusiasm with less knowledgeable friends".

Dr. Waterman leaves a widow.

Notes and News

TOWARDS CLEANER AIR

INDUSTRY was praised for its efforts to reduce air pollution in a presidential address by Sir Hugh Beaver to the Clean Air Conference held in Harrogate on Oct. 5–7 by the National Society for Clean Air. Industry, Sir Hugh said, had already spent or allocated several million pounds for clean air measures. As regards domestic smoke, heating appliances which could safely use many of our raw coals without nuisance and without skilled, or at least without skilful, and continuous attention had not yet been developed. " So if we believe in clean air, if we believe that too long have we subjected ourselves and our children and our aged to the unquestioned and lethal dangers of foul air, we must accept that there must in due course be some control over all domestic firing appliances wherever people are thickly congregated, or over the fuel used—or both." In industry it was possible to use in nearly all boilers and furnaces the poorest of coals so as reasonably to fall within the Clean Air Act. With the domestic hearth this was not so, and probably never could be so. At a later session Mr. F. P. Williams declared that nowadays almost all the smoke came from domestic fires, and that the observed pollution was not connected with the size of the town: pollution was a much more local matter than had previously been thought. Mr. E. M. Birtwhistle remarked that smoke issuing from a chimney was money being thrown away: " smoke and inefficiency are great companions."

BOARD OF CONTROL

THE Board of Control, the central Government department which with the Minister of Health shares the responsibilities for mentally disordered patients, is to be dissolved in November under the provisions of the Mental Health Act, 1959. It was set up under the Mental Deficiency Act, 1913, and took over the functions under the Lunacy Acts previously performed by the Lunacy Commissioners. Since the National Health Service came into being the Board has been responsible, broadly speaking, for matters affecting individual patients and the procedures applied to them, especially the procedures which authorise detention. Some of these functions will in future be carried out by the Minister of Health and the hospital and local health authorities, while others will be discharged by the mental health review tribunals set up under the new Act.

In its last report,[1] the Board notes the encouraging trend in admissions on a voluntary basis. In 88% of all direct admissions for treatment in 1959, compulsory powers were not used. This proportion included 16,724 patients (17%) received for treatment on an informal basis during the last three months of the year under the first commencement order made under the new Act. The Board is hopeful that this long-established trend will continue.

ELDERLY FEET

SINCE 1955 the National Corporation for the Care of Old People have been offering voluntary committees grants for chiropody services in exchange for records of such practical items as numbers of patients and treatments and cost. Their foresight has been justified, for last year the Minister of Health empowered local health authorities to set up chiropody services, and the corporation are now able to provide some practical advice [2] based on their barter of grants for records.

They admit frankly that they are disappointed that the new powers given to the authorities are only permissive. They fear that, because of shortage of staff and the block grant, many authorities will hesitate to use them. Those that do will probably run their service from their own clinics, though they may if they wish subsidise voluntary schemes. In the corporation's view in many districts this second arrangement would have much to commend it. Where there is a shortage of chiropodists and where there are opportunities for private practice, a clinic-based service with modest sessional rates or full-time salaries is unlikely to attract many chiropodists. But some might be willing to accept N.H.S. patients if they were allowed to treat them in their own surgeries.

Among other points which the corporation put forward for consideration is the decision where a patient should be treated. Many clinics, and some private surgeries, are not on the ground floor. Some are not easily accessible by public transport. The elderly patient in need of chiropody is usually neither agile nor very mobile. An awkward staircase or an awkward bus journey may prove an insuperable barrier to treatment. Indeed, in some country areas an adequate service can probably be provided only by domiciliary visits.

The corporation are not able to offer firm estimates about costs to guide the organisers of official services, for many chiropodists reduced their charges for the voluntary schemes taking part in the survey. Clearly an adequate chiropody service is going to add considerably to local-authority expenditure, but the corporation are convinced that it is a necessity for many elderly people and might lessen their demand on other health and welfare services—" painful feet leading to inability to get about easily may well prove to be the beginning of physical deterioration ". This opinion is backed by Dr. A. N. Exton-Smith's assessment of the value of chiropody to 120 elderly patients whom he examined. According to his survey (published as an appendix to the report), to all the patients it had proved of " great benefit as regards physical comfort, the maintenance of mobility, and improvement in morale ".

1. Annual Report for the year 1959 of the Board of Control to the Lord Chancellor. H.M. Stationery Office. 1960. 9*d*.
2. Chiropody for the Elderly: a three-year study of 120 voluntary schemes. 1960. Pp. 44. 2*s*. (From the Corporation, Nuffield Lodge, Regent's Park, London, N.W.1.)

University of London

At recent examinations for the D.C.P. the following were successful:

E. C. Christian, J. L. Grech, Bodh Krishna Jha, H. J. Koornhof, H. G. McDonald, J. B. MacGillivray, Rohma Newman, W. H. Payne, M. J. Phillips, Mohammed Qudratullah, Said Mohamad Sadique, Julian Shapiro, Ijenwa Osita Kanayo Udeozo, Dona Priyalatha Wijesinghe, Kishwar Zahur-Ud-Din.

Royal College of Obstetricians and Gynæcologists

Mr. Ian MacGillivray will give a William Blair-Bell lecture on Friday, Oct. 28, at 5 P.M., at the college, 27, Sussex Place, Regent's Park, London, N.W.1. He will speak on hypertension in pregnancy and its consequences.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the faculty on Oct. 3, with Mr. Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship:

J. H. Dagg, *qua physician*; Padma Pannala Reddy, N. V. Sweeney, *qua surgeon*.

Ciba Foundation Lectures

Prof. J. Konorski, of the Nencki Institute of Experimental Biology of Warsaw, will give a lecture on Friday, Nov. 4, at 5 P.M., at the Royal Institute of British Architects, 66, Portland Place, London, W.1. His subject will be changing concepts concerning physiological mechanisms of animal motor behaviour. Dr. P. J. Thung, of Antonie van Leeuwenhoek-Huis of Amsterdam, will give a lecture on Thursday, Nov. 24, at 5 P.M., at the Medical School, Edgbaston, Birmingham. He will speak on ageing in the gonad-adrenal system.

Tropical Medicine Research Board

As announced in their last annual report, the Medical Research Council are setting up a Tropical Medicine Research Board to advise them on the promotion and coordination of all research in this field. The membership of the board, which has been decided after consultation with the Colonial Office and Commonwealth Relations Office, is as follows:

Sir Harold Himsworth (chairman), Prof. A. C. Frazer (vice-chairman), Sir John Boyd, Prof. P. C. C. Garnham, Prof. W. E. Kershaw, Dr. Raymond Lewthwaite, Prof. George Macdonald, Prof. B. G. Maegraith, Prof. B. S. Platt, Prof. M. L. Rosenheim, Mr. H. J. Seddon, Prof. E. T. C. Spooner, Prof. A. W. Woodruff, and Dr. B. S. Lush (secretary).

The Chief Medical Officer and the head of the research department of the Colonial Office have been appointed assessors, and two assessors have been nominated by the Secretary of State for Commonwealth Relations.

University College, London

Mr. A. F. Huxley, F.R.S., will give his inaugural lecture as Jodrell professor of physiology on Tuesday, Nov. 29, at 5.30 P.M., at the college, Gower Street, W.C.1. His subject will be theories of muscular contraction.

International Congress on Keratoplasty

This congress is being held in Prague from Oct. 19 to 21. The speakers from this country will be Sir Tudor Thomas and Sir Benjamin Rycroft.

Prof. Ruth Bowden has been elected chairman of the council of the Chartered Society of Physiotherapy in succession to Sir Harold Boldero, who is retiring after having served for six years.

Mr. Austin Concanon and Dr. R. E. Angel are visiting Barcelona and Madrid from Nov. 14 to 21 at the invitation of the Asociacion de Obstetricia y Ginecologia of Barcelona, and Prof. J. Botella of the Institute of Obstetrics and Gynæcology in Madrid.

A meeting of the Biochemical Society will be held on Saturday, Oct. 22, at 10.25 A.M., at the National Institute for Medical Research, The Ridgeway, Mill Hill, London, N.W.7.

At the Midland Centre for Neurosurgery, Holly Lane, Smethwick, on Oct. 27 at 8 P.M., Dr. Gunnar Brante of Eskilstuna, Sweden, will give a lecture on some aspects of the composition of nervous tissue and its alteration in disease.

The annual dinner of the Society for the Study of Addiction is to be held at the Rembrandt rooms, Thurloe Place, London, S.W.7, on Oct. 17, at 7.30 P.M. The chief guest will be Mr. A. Dickson Wright. Tickets (25*s.*) may be had from Dr. Ellis Stungo, 93, Harley Street, W.1.

Helping the Elderly to Live at Home.—In this booklet Dr. Kenneth Hazel, consultant gerontologist to Wolverhampton and Walsall, gives some useful hints to relatives or neighbours who are looking after an old person in his own home. Copies (2*s.*, postage 4*d.*) may be had from the Central Council for Health Education, Tavistock House North, London, W.C.1.

Appointments

BARRY, J. V., M.B.: deputy director (S.H.M.O.), Glasgow and West of Scotland transfusion region, with headquarters at Law Hospital, Carluke.
ENOCH, M. D., M.R.C.S., D.P.M.: S.H.M.O., Runwell Hospital, Wickford.
EVANS, AUDREY TREVOR, M.R.C.S., D.P.H.: M.O., London County Council.
ISAAC, R. G., M.R.C.S.: M.O., London County Council.
LOCKHART-MUMMERY, H. E., M.D., M.CHIR. Cantab., F.R.C.S.: surgeon, St. Thomas's Hospital, London.
MACARA, A. W., M.B. Glasg., D.P.H.: assistant M.O., school health and maternal and child welfare services, Bristol.
SHEERBOOM, D. J., M.B. Lond., D.P.H.: deputy M.O.H., Kensington, London.
WATKINSON, GEOFFREY, M.D. Lond., M.R.C.P.: part-time consultant in general medicine, York area.

The Hospital for Sick Children, Great Ormond Street, London:

ABERDEEN, EOIN, M.B. Melb., F.R.C.S., D.C.H.: surgical first assistant to the cardio-thoracic unit.
DINGLE, H. R., B.M. Oxon.: resident anæsthetic registrar, Tadworth.
FERRY, ANNA A., M.B. Sydney: house-physician.
HARRIS, DOROTHY E., M.B. Lond., F.F.A. R.C.S., D.A.: junior resident anæsthetist.
LOWE, L. W., M.B. Leeds: house-surgeon.
SARKAR, SATYABRATA, M.B. Calcutta, D.L.O.: senior E.N.T. registrar.
SCOTT, K. E., M.D.: house-physician.
SHEVILLE, ELI, M.B. Glasg., D.M.R.D.: registrar in radiology.
STIMMLER, LEO, M.B. Lond., M.R.C.P.: house-physician.

Birmingham Regional Hospital Board:

FOSTER, W. D., M.D. Cantab.: consultant pathologist, Birmingham (Dudley Road) group of hospitals.
KELLOCK, I. A., M.D. Lond., M.R.C.P.: consultant physician (geriatrics), Birmingham (Dudley Road) group of hospitals.
LUMB, PATRICIA M., M.B. Birm., F.F.A. R.C.S., D.A.: part-time consultant anæsthetist, United Birmingham Hospitals and the Birmingham (Selly Oak) and Birmingham (Sanatoria) group of hospitals.
PATHY, M. S., M.R.C.P.E.: consultant physician (geriatrics), Coventry group of hospitals.
SMITH, A. J., M.D. Lond., D.PATH.: part-time consultant pathologist, Coventry group of hospitals.
STUART, D. W., M.B. Lond., F.R.C.S., D.L.O.: part-time consultant E.N.T. surgeon, Stoke-on-Trent group of hospitals.

Sheffield Regional Hospital Board:

ACKERLEY, A. G., M.B. Cantab., F.R.C.S., D.L.O.: consultant pathologist, Leicester group of hospitals.
ARKLE, J. K., M.B. Durh., D.P.M.: senior assistant psychiatrist, Pastures Hospital, Mickleover, near Derby.
SEARS, R. T., M.B. Cantab., F.R.C.S., M.R.C.O.G.: part-time consultant obstetrician and gynæcologist, Nottingham and Mansfield area hospitals.

Diary of the Week

OCT. 16 TO 22

Monday, 17th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. A. R. Currie: Modern Aspects of Thyroid Pathology.
POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Dr. John Marshall: Present Status of Therapy in Cerebrovascular Disease.

Tuesday, 18th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
3 P.M. Sir Francis Fraser: Challenge to the Medical Profession. (Harveian oration.)
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright Fleming Institute.) Dr. Gordon Mitchell-Heggs: Pruritus vulvæ.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. A. D. Gordon: Stereotaxis.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. J. D. S. Cameron: Aspects of Hepatic Disease.
SOCIETY FOR THE STUDY OF ADDICTION
8 P.M. (11, Chandos Street, W.1.) Dr. Abraham Walker (Lexington, Kentucky): Nature of Addiction and Habituation.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. J. D. Spillane: New Dimensions in Neurology.

Wednesday, 19th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Comparative Medicine.* Dr. J. M. Alston: Recent Developments in Leptospirosis. (Presidential address.)
8.15 P.M. *General Practice.* Dr. R. J. F. H. Pinsent: Art and Science in General Practice. (Valedictory address.)
POSTGRADUATE MEDICAL SCHOOL
2 P.M. Dr. Kenneth Lowe: Tests of Renal Function.
ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. L. N. Katz (Chicago): Recent Advances in the Management of Atherosclerosis.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
5 P.M. Dr. W. A. R. Thomson: Doctors, Drugs, and Diseases. (Bengué lecture.)
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Arthur Tickner: Biochemistry of Skin Diseases.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. V. H. Springett: Tuberculosis Epidemiology and Methods of Control.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Dr. John Marshall, Dr. R. A. Beaver, Dr. J. B. L. Howell: Symposium on Management of Respiratory Emergencies.
MIDLAND MEDICAL SOCIETY
8.45 P.M. (Birmingham Medical Institute, 36, Harborne Road, Edgbaston.) Prof. M. Stacey: Alchemy—Ancient and Modern.
UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds.) Mr. Herbert Agar: Irregular Bleeding at Climacteric.
6 P.M. Mr. G. W. Theobald: Significance of Antenatal Clinics and Antenatal Beds.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh, 8
3.30 P.M. Mr. Eric Samuel: Mechanical Syndromes following Partial Gastrectomy.

Thursday, 20th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Prof. J. F. Nuboer: Recurrent Peptic Ulcer after Gastrectomy. (Moynihan lecture.)
UNIVERSITY OF LONDON
5 P.M. (Royal Veterinary College, Royal College Street, N.W.1.) Prof. C. W. Emmens (Sydney): Effects of Anti-œstrogens.
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (Senate House, Malet Street, W.C.1.) Prof. C. H. Waddington: Significance of Developmental Biology.
BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. J. W. D. Bull: History of Neuroradiology. (Presidential address.)
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics.* Dr. James Sneddon: Presidential address.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Dr. C. C. Booth: Studies in Intestinal Absorption and Malabsorption.

Friday, 21st

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Sir George Pickering, Sir Robert Platt: Nature of Essential Hypertension.
8.15 P.M. *Radiology.* Dr. E. B. D. Neuhauser (Boston): Lesions Derived from Neuro-enteric Canals.
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Dr. B. G. B. Lucas: Physiological Aspects of Anæsthesia.
4 P.M. Dr. J. F. Goodwin: Cardiomyopathy.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Miss Edith Whetnall: Deaf Child.
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Dr. Michael Balint: Examination by the Patient.
MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Joint meeting with Royal Medico-Chirurgical Society of Glasgow, 242, St. Vincent Street, Glasgow, C.2.) Dr. W. M. Harrowes, Dr. Gavin Arneil, Dr. B. E. C. Nordin, Mr. James Ross: That the Practice of Medicine is an Antisocial Activity.